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(51) International Patent Classification ⁶ : C07D 205/08, A61K 31/395	A1	(11) International Publication Number: WO 99/18072 (43) International Publication Date: 15 April 1999 (15.04.99)
(21) International Application Number: PCT/CA98/00953 (22) International Filing Date: 6 October 1998 (06.10.98) (30) Priority Data: 60/061,544 7 October 1997 (07.10.97) US (71) Applicant (for all designated States except US): BOEHRINGER INGELHEIM (CANADA) LTD. [CA/CA]; 2100 Cunard, Laval, Quebec H7S 2G5 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): YOAKIM, Christiane [CA/CA]; 65 Gianchetti, Laval, Quebec H7G 4T5 (CA). DEZIEL, Robert [CA/CA]; 546 avenue Chester, Ville Mont-Royal, Quebec H3R 1W9 (CA). OGILVIE, William, W. [CA/CA]; 335 rue Edgewood, Rosemere, Quebec J7A 2M3 (CA). O'MEARA, Jeffrey [CA/CA]; 590 rue Jolivet #4, Laval-des-Rapides, Quebec H7N 5Y6 (CA). (74) Agents: TANDAN, Susan, I. et al.; Van Zant & Associates, Suite 1407, 77 Bloor Street West, Toronto, Ontario M5S 1M2 (CA).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: AZETIDINONE DERIVATIVES FOR THE TREATMENT OF HCMV INFECTIONS (57) Abstract <p>A compound of formula (I) wherein R¹ is hydrogen, methyl, ethyl, methoxy or methylthio; R² and R³ each independently is hydrogen or lower alkyl; R⁴ is hydrogen, lower alkyl, methoxy, ethoxy or benzyloxy; R⁵ is lower alkyl, lower cycloalkyl, (CH₂)_mC(O)OR⁶ wherein m is the integer 1 or 2 and R⁶ is lower alkyl, phenyl optionally substituted; optionally Het or Het(lower alkyl); or R⁴ and R⁵ together with the nitrogen atom to which they are attached form a nitrogen containing ring optionally substituted with C(O)O-benzyl or with phenyl optionally substituted with C(O)OR₇ wherein R₇ is lower alkyl or (lower alkyl)phenyl; and Z is lower alkyl or optionally substituted phenyl or Het; with the proviso that when Z is (CH₂)_p-(Het), then R² and R³ each is hydrogen; or a therapeutically acceptable acid addition salt thereof.</p> <div style="text-align: center;"> <p>(I)</p> </div>		

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AZETIDINONE DERIVATIVES FOR THE TREATMENT OF
HCMV INFECTIONS

Field of the Invention

5

This invention relates to azetidinone derivatives having activity against herpes infections. More specifically, the invention relates to azetidin-2-one derivatives exhibiting antiherpes activity, to
10 pharmaceutical compositions comprising the derivatives, and methods of using the derivatives to inhibit the replication of herpes virus and to treat herpes infections.

15 Background of the Invention

Herpes viruses inflict a wide range of diseases against humans and animals. For instance, herpes simplex viruses, types 1 and 2 (HSV-1 and HSV-2), are
20 responsible for cold sores and genital lesions, respectively; varicella zoster virus (VZV) causes chicken pox and shingles; and the human cytomegalovirus (HCMV) is a leading cause of opportunistic infections in immunosuppressed
25 individuals.

Over the past two decades, a class of compounds known as the purine and pyrimidine nucleoside analogs has received the most attention by investigators in the
30 search for new therapeutic agents for treatment of herpes virus infections. As a result, several nucleoside analogs have been developed as antiviral agents. The most successful to date is acyclovir which is the agent of choice for treating genital HSV

infections. Another nucleoside analog, ganciclovir, has been used with some success in treating HCMV infections.

- 5 Nevertheless, in spite of some significant advances, the need for effective, safe therapeutic agents for treating herpes viral infections continues to exist. For a review of current therapeutic agents in this area, see R.E. Boeheme et al., Annual Reports in
10 Medicinal Chemistry, 1995, 30, 139.

The present application discloses a group of azetidin-2-one derivatives particularly active against cytomegalovirus. This activity coupled with
15 a wide margin of safety, renders these derivatives desirable agents for combating herpes infections.

Azetidin-2-one derivatives have been reported in the literature as having a variety of biological
20 activities; mainly antibacterial, antiinflammatory, antidegenerative, etc. However, azetidin-2-one derivatives have not been reported to be antiviral agents against herpes viruses.

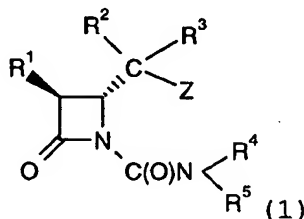
- 25 The following references disclose azetidin-2-ones having biological activity:

S.K. Shah et al., European patent application
0,199,630, October 29, 1986,
S.K. Shah et al., European patent application
30 0,377,549, October 18, 1989,
P.L. Durette and M. Maccoss, US patent 5,100,880,
March 31, 1992,
P.L. Durette and M. Maccoss, US patent 5,104,862,
April 14, 1992,

- W.K. Hagmann et al., *Bioorg. Med. Chem. Lett.* **1992**, 2, 681,
W.K. Hagmann et al., *J. Med. Chem.* **1993**, 36, 771,
J.B. Doherty et al., US patent 5,229,381, issued July
5 20, 1993,
S.K. Shah et al., *Bioorg. Med. Chem. Lett.* **1993**, 3, 2295,
G. Crawley, PCT patent WO 95/02579, published January 26, 1995,
10 P.E. Finke et al., *J. Med. Chem.* **1995**, 38, 2449, and
K. Kobayashi et al., Japanese patent application 07242624, published September 19, 1995; *Chem. Abstr.* **1996**, 124, 29520.
- 15 The present azetidin-2-one derivatives are distinguished from the prior art compounds in that they possess different chemical structures and biological activities.

20 Summary of the Invention

The azetidin-2-one derivatives are represented by formula 1:



- 25 wherein R^1 is hydrogen, methyl, ethyl, methoxy or methylthio;
 R^2 and R^3 each independently is hydrogen or lower alkyl;
 R^4 is hydrogen, lower alkyl, methoxy, ethoxy or
30 benzyloxy;

- R^5 is lower alkyl, lower cycloalkyl, $(CH_2)_mC(O)OR^6$ wherein m is the integer 1 or 2 and R^6 is lower alkyl or phenyl(lower alkyl);
- phenyl, phenyl monosubstituted, disubstituted or
- 5 trisubstituted with a substituent selected independently from the group consisting of lower alkyl, lower alkoxy, lower alkylthio, halo, hydroxy and amino; phenyl(lower alkyl), phenyl(lower alkyl) monosubstituted or disubstituted on the phenyl
- 10 portion thereof with a substituent selected independently from the group consisting of lower alkyl, lower alkoxy, lower alkylthio, halo, hydroxy, nitro, amino, lower alkylamino, di(lower alkyl)amino, lower acylamino, di(lower alkyl)aminocarbonyl, cyano,
- 15 trifluoromethyl, (trifluoromethyl)thio, (trifluoromethyl)sulfinyl, (trifluoromethyl)sulfonyl and $C(O)OR^7$ wherein R^7 is lower alkyl or phenyl(lower alkyl);
- Het or Het(lower alkyl) wherein Het represents an
- 20 unsubstituted, monosubstituted or disubstituted five or six membered, monovalent heterocyclic ring containing one or two heteroatoms selected from the group consisting of N, O or S, wherein each substituent is selected independently from the group
- 25 consisting of lower alkyl, lower alkoxy, halo and hydroxy;
- 5-(benzo[1,3]dioxolyl) methyl, (1(R)-1-naphthalenyl)ethyl, 2-benzothiazolyl or 2-thiazolo[4,5-b]pyridinyl; or
- 30 R^4 and R^5 together with the nitrogen atom to which they are attached form a piperidino, morpholino, thiomorpholino, piperazino, N-methylpiperazino, 1-(3,4-dihydro-1H-isoquinolinyl) or 2-(3,4-dihydro-1H-isoquinolinyl) or a pyrrolidino ring optionally

substituted with benzyloxycarbonyl or with phenyl
said phenyl ring optionally mono- or
di-substituted with a substituent selected
independently from the group consisting of lower
5 alkyl, lower alkoxy, lower alkylthio, halo, hydroxy,
nitro, amino, lower alkylamino, di(lower alkyl)amino,
lower acylamino, di(lower alkyl)aminocarbonyl, cyano,
trifluoromethyl, (trifluoromethyl)thio,
(trifluoromethyl)sulfinyl, (trifluoromethyl)sulfonyl
10 and C(O)OR₇, wherein R₇ is lower alkyl or (lower
alkyl)phenyl;
and
Z is lower alkyl, phenyl, phenyl monosubstituted or
disubstituted with a substituent selected
15 independently from lower alkyl, lower alkoxy, halo,
hydroxy and amino; phenylmethyl, phenylmethyl mono-
substituted or disubstituted on the phenyl portion
thereof with a substituent selected from the group
consisting of lower alkyl, lower alkoxy, halo,
20 hydroxy and amino; or (CH₂)_p-(Het) wherein p is the
integer 0 or 1 and Het is as defined herein; with the
proviso that when Z is (CH₂)_p-(Het) as defined herein
then R² and R³ each is hydrogen;
or a therapeutically acceptable acid addition salt
25 thereof.

A preferred group of compounds is represented by
formula 1 wherein R¹, R² and R³ are as defined
hereinabove;
30 R⁴ is hydrogen or lower alkyl;
R⁵ is lower alkyl, lower cycloalkyl, CH₂C(O)OR⁶
wherein R⁶ is methyl, ethyl or phenylmethyl; phenyl,
phenyl monosubstituted, disubstituted or

trisubstituted with a substituent selected independently from the group consisting of lower alkyl, lower alkoxy, lower alkylthio, halo, hydroxy and amino; phenyl(lower alkyl), phenyl(lower alkyl) 5 monosubstituted or disubstituted on the phenyl portion thereof with a substituent selected independently from the group consisting of lower alkyl, lower alkoxy, lower alkylthio, halo, hydroxy, nitro, amino, lower alkylamino, di(lower alkyl)amino, 10 lower acylamino, di(lower alkyl)aminocarbonyl, cyano, trifluoromethyl, (trifluoromethyl)thio, (trifluoromethyl)sulfinyl, (trifluoromethyl)sulfonyl and C(O)OR⁷ wherein R⁷ is methyl, ethyl or phenylmethyl; Het or Het(lower alkyl) wherein Het is 15 2-furyl, 2-methyl-3-furyl, 2-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 3-methyl-2-pyrrolyl, 2-thiazolyl, 4-thiazolyl, 2-isoxazolyl, 2-pyrimidinyl, 4-methyl-2-pyrimidinyl, 4,6-dimethyl-2-pyrimidinyl, 4-pyrimidinyl, 2,6-dimethyl-2-pyrimidinyl, 4-methyltetrazolyl, 2-benzothiazolyl or 2-thiazolo[4,5-b]pyridinyl; (5-benzo[1,3]dioxolyl)methyl, 1(R)-(1-naphthalenyl)ethyl; or 20 R⁴ and R⁵ together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino, N-methylpiperazino, 1-(3,4-dihydro-1H-isoquinolinyl) or 2-(3,4-dihydro-1H-isoquinolinyl); and Z is as defined hereinabove.

A more preferred group of compounds is represented by 30 formula 1 wherein R¹ is hydrogen, methyl, ethyl, methoxy or methylthio; R² and R³ each independently is hydrogen, or methyl; R⁴ is hydrogen, methyl, or ethyl;

R^5 is methyl, ethyl, 1-methylethyl, cyclobutyl, cyclopentyl, cyclohexyl, $CH_2C(O)OR^6$ wherein R^6 is methyl or phenylmethyl; phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,5-dimethyl-4-methoxyphenyl, 4-methylphenyl, 4-(methylthio)phenyl, phenylmethyl, phenylethyl, 1-phenylpropyl, 1-phenylbutyl, phenylmethyl monosubstituted at position 3 or 4 of the phenyl portion thereof with a substituent selected from the group consisting of methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, methoxy, ethoxy, methylthio, bromo, chloro, fluoro, nitro, acetylamino, $C(O)NMe_2$, $C(O)NEt_2$, cyano, trifluoromethyl, (trifluoromethyl)thio, (trifluoromethyl)sulfinyl, (trifluoromethyl)sulfonyl and $C(O)OR^7$ wherein R^7 is methyl, ethyl or benzyl; (5-benzo[1,3]dioxolyl)methyl, 1(R)-(1-naphthylene)ethyl, 2-pyridinyl, 4-pyridinyl, 2-pyridinylmethyl, 4-pyridinylmethyl, 1-(4-pyridinyl)ethyl or 1-(4-pyridinyl)propyl; or R^4 and R^5 together with the nitrogen to which they are attached form a pyrrolidino, piperidino, morpholino, 1-(3,4-dihydro-1H-isoquinolinyl) or 2-(3,4-dihydro-1H-isoquinolinyl); and Z is phenyl or phenylmethyl.

25

Another more preferred group of compounds is represented by formula 1 wherein R^1 is hydrogen, methyl or methylthio; R^2 and R^3 each independently is hydrogen or methyl; R^4 is hydrogen, methyl or ethyl; R^5 is methyl, ethyl, 1-methylethyl, cyclobutyl, cyclopentyl, cyclohexyl, $CH_2C(O)OR^6$ wherein R^6 is

30

- methyl or phenylmethyl; phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,5-dimethyl-4-methoxyphenyl, 4-methylphenyl, 4-(methylthio)phenyl, phenylmethyl, 1-phenylpropyl, 1-phenylbutyl, phenylmethyl mono-
- 5 substituted at position 3 or 4 of the phenyl portion thereof with a substituent selected from the group consisting of methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, methoxy, ethoxy, methylthio, bromo, chloro, fluoro, nitro, acetylamino, C(O)NMe₂,
- 10 C(O)NEt₂, cyano, trifluoromethyl, (trifluoromethyl)thio, (trifluoromethyl)sulfinyl, (trifluoromethyl)sulfonyl and C(O)OR⁷ wherein R⁷ is methyl, ethyl or benzyl; (5-benzo[1,3]dioxolyl)methyl, 1(R)-(1-
- 15 naphthalenyl)ethyl, 2-pyridinyl, 4-pyridinyl, 2-pyridinylmethyl, 4-pyridinylmethyl, 1-(4-pyridinyl)ethyl or 1-(4-pyridinyl)propyl; and Z is lower alkyl.
- 20 Still another more preferred group of compounds is represented by formula 1 wherein R¹ is hydrogen, methyl, methylthio or methoxy; R² and R³ each independently is hydrogen or methyl; R⁴ is hydrogen, methyl or ethyl;
- 25 R⁵ is methyl, ethyl, 1-methylethyl, cyclobutyl, cyclopentyl, cyclohexyl, CH₂C(O)OR⁶ wherein R⁶ is methyl or phenylmethyl; phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,5-dimethyl-4-methoxyphenyl, 4-methylphenyl, 4-(methylthio)phenyl, phenylmethyl, 1-
- 30 phenylpropyl, 1-phenylbutyl, phenylmethyl mono-substituted at position 3 or 4 of the phenyl portion thereof with a substituent selected from the group consisting of methyl, ethyl, 1-methylethyl, 1,1-

dimethylethyl, propyl, methoxy, ethoxy, methylthio, bromo, chloro, fluoro, nitro, acetylamino, C(O)NMe₂, C(O)NEt₂, cyano, trifluoromethyl, (trifluoromethyl)thio, (trifluoromethyl)sulfinyl, (trifluoromethyl)sulfonyl and C(O)OR⁷ wherein R⁷ is methyl, ethyl or benzyl; (5-benzo[1,3]dioxolyl)methyl, 1(R)-(1-naphthalenyl)ethyl, 2-pyridinyl, 4-pyridinyl, 2-pyridinylmethyl, 4-pyridinylmethyl, 1-(4-pyridinyl)ethyl or 1-(4-pyridinyl)propyl; and Z is 2-furyl, 2-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 3-methyl-2-pyrrolyl, 2-thiazolyl, 2-isoxazolyl, 2-pyrimidinyl, 4,6-dimethyl-2-pyrimidinyl, 5-(1-methyl-1H-tetrazolyl), 5-(2-methyl-2H-tetrazolyl), 2-benzothiazolyl or 2-thiazolo[4,5-b]pyridinyl.

A most preferred group of compounds is represented by formula 1 wherein R¹ is hydrogen, methyl, methoxy or methylthio;

R² and R³ each is hydrogen;

R⁴ is hydrogen or methyl;

R⁵ is CH₂C(O)OR⁶ wherein R⁶ is phenylmethyl; or

R⁵ is 4-fluorophenyl, 4-methoxyphenyl, 3,5-dimethyl-4-methoxyphenyl, (4-methylthio)phenyl, phenylmethyl, 1(R)-phenylethyl, 1(S)-phenylethyl, 1(R)-phenylpropyl, 1(R)-phenylbutyl, (4-methylphenyl)methyl, {4-(1-methylethyl)phenyl}methyl, (4-methoxyphenyl)methyl, (4-chlorophenyl)methyl, (2-nitrophenyl)methyl, (3-nitrophenyl)methyl, {4-(acetylamino)phenyl}methyl, {4-(trifluoromethyl)phenyl}methyl, {4-((trifluoromethyl)thio)phenyl}methyl, {4-

{(trifluoromethyl)sulfinyl}phenyl)methyl, {4-
{(trifluoromethyl)sulfonyl}phenyl)methyl, {4-
(methoxycarbonyl)phenyl} methyl, (5-benzo[1,3]
dioxolyl)methyl, 1(R)-(1-naphthalenyl)ethyl, 4-
5 pyridinyl, 4-pyridinylmethyl or 1-(4-
pyridinyl)propyl; or
 R^4 and R^5 together with the nitrogen to which they
are attached form a pyrrolidino, morpholino, 1-(3,4-
dihydro-1H-isoquinolinyl) or 2-(3,4-dihydro-1H-
10 isoquinolinyl); and
 Z is phenyl or phenylmethyl.

Included within the scope of this invention is a
pharmaceutical composition for treating
15 cytomegalovirus infections in a human comprising a
compound of formula 1, or a therapeutically
acceptable salt thereof, and a pharmaceutically
acceptable carrier.

20 The scope of the invention also includes a method for
treating cytomegalovirus infections in a human
comprising administering thereto an effective amount
of the compound of formula 1, or a therapeutically
acceptable salt thereof.

25 Also included within the scope is a method for
protecting human cells against cytomegalovirus
pathogenesis comprising treating said cells with an
anti-cytomegalovirus effective amount of a compound
30 of formula 1, or a therapeutically acceptable salt
thereof.

Compounds of formula I according to the present
invention may also be used in co-therapies with other
35 conventional anti-herpes compounds, such as but not

limited to ganciclovir, foscarnet, acyclovir, valacyclovir, famciclovir, cidofovir, penciclovir, and lobucavir.

- 5 Compounds of formula I according to the present invention may also be used in co-therapies with anti-retroviral compounds such as reverse transcriptase inhibitors (i.e. AZT, 3TC) or protease inhibitors.
- 10 Process for preparing the compounds of formula 1 are described hereinafter.

Detailed Description of the Invention

15 General

As used herein, the following definitions apply unless otherwise noted:

- With reference to the instances where (R) or (S) is
20 used to designate the configuration of a radical, e.g. R⁵ of the compound of formula 1, the designation is done in the context of the compound and not in the context of the radical alone.

- 25 The term "residue" with reference to an amino acid or amino acid derivative means a radical derived from the corresponding α -amino acid by eliminating the hydroxyl of the carboxy group and one hydrogen of the α -amino group. For instance, the terms Gln, Ala, Gly,
30 Ile, Arg, Asp, Phe, Ser, Leu, Cys, Asn, Sar and Tyr represent the "residues" of L-glutamine, L-alanine, glycine, L-isoleucine, L-arginine, L-aspartic acid, L-phenylalanine, L-serine, L-leucine, L-cysteine, L-asparagine, sarcosine and L-tyrosine, respectively.

The term "side chain" with reference to an amino acid or amino acid derivative means a residue attached to the α -carbon atom of the α -amino acid. For example,
5 the R-group side chain for glycine is hydrogen, for alanine it is methyl, for valine it is isopropyl. For the specific R-groups or side chains of the α -amino acids reference is made to A.L. Lehninger's text on Biochemistry (see chapter 4).

10

The term "halo" as used herein means a halo radical selected from bromo, chloro, fluoro or iodo.

The term "lower alkyl" or (C_{1-6} alkyl) as used herein,
15 either alone or in combination with another radical, means straight or branched chain alkyl radicals containing up to six carbon atoms and includes methyl, ethyl, propyl, butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl.

20

The term "lower alkoxy" as used herein means straight chain alkoxy radicals containing one to four carbon atoms and branched chain alkoxy radicals containing three to four carbon atoms and includes methoxy,
25 ethoxy, propoxy, 1-methylethoxy, butoxy and 1,1-dimethylethoxy. The latter radical is known commonly as *tert*-butoxy.

The term "lower alkanoyl" as used herein, either
30 alone or in combination with another radical, means a straight chain 1-oxoalkyl containing from one to six carbon atoms or a branched chain 1-oxoalkyl containing from four to six carbon atoms; for example, acetyl, propionyl(1-oxopropyl), 2-methyl-1-oxopropyl, 2-methylpropionyl and 2-ethylbutyryl.
35

The term "lower cycloalkyl" as used herein, either alone or in combination with another radical, means saturated cyclic hydrocarbon radicals containing from
5 three to seven carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "amino" as used herein means an amino radical of formula $-NH_2$. The term "lower alkylamino"
10 as used herein means alkylamino radicals containing one to six carbon atoms and includes methylamino, propylamino, (1-methylethyl)amino and (2-methylbutyl)amino. The term "di(lower alkyl)amino" means an amino radical having two lower alkyl
15 substituents each of which contains one to six carbon atoms and includes dimethylamino, diethylamino, ethylmethylamino and the like.

The term "Het" as used herein means a monovalent
20 radical derived by removal of a hydrogen from a five- or six-membered saturated or unsaturated heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur. Optionally, the heterocycle may bear one or two substituents; for
25 example, *N*-oxido, lower alkyl, phenyl-(C_{1-3})alkyl, lower alkoxy, halo, amino or lower alkylamino. Again optionally, the five- or six- membered heterocycle can be fused to a phenyl. Examples of suitable heterocycles and optionally substituted heterocycles
30 include pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, 1*H*-imidazole, 1-methyl-1*H*-imidazole, pyrazole, furan, thiophene, oxazole, isoxazole, thiazole, 2-methylthiazole, 2-aminothiazole, 2-(methylamino)-thiazole, piperidine, 1-
35 methylpiperidine, 1-methylpiperazine, 1,4-dioxane,

morpholine, pyridine, pyridine *N*-oxide, pyrimidine, 2,4-dihydroxypyrimidine, 2,4-dimethylpyrimidine, 2,6-dimethylpyrimidine, 1-methyl-1*H*-tetrazole, 2-methyl-2*H*-tetrazole, benzothiazole and thiazolo[4,5-
5 b]pyridine.

The term "pharmaceutically acceptable carrier" as used herein means a non-toxic, generally inert vehicle for the active ingredient which does not
10 adversely affect the ingredient.

The term "effective amount" means a predetermined antiviral amount of the antiviral agent, i.e. an amount of the agent sufficient to be effective
15 against the virus *in vivo*.

The azetidin-2-one derivatives of formula 1 can be obtained in the form of therapeutically acceptable acid addition salts. In the instance where a
20 particular derivative has a residue which functions as a base, examples of such salts are those with organic acids, e.g. acetic, lactic, succinic, benzoic, salicylic, methanesulfonic or *p*-toluenesulfonic acid, as well as polymeric acids such
25 as tannic acid or carboxymethyl cellulose, and salts with inorganic acids such as hydrohalic acids, e.g. hydrochloric acid, or sulfuric acid, or phosphoric acid.

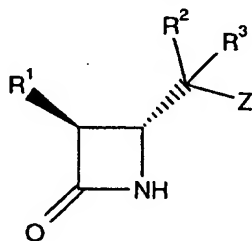
30 Process

Compounds of formula 1 can be synthesized from commercially available, suitably protected amino acids, as exemplified hereinafter. (For general
35 synthetic procedures see: *The Organic Chemistry of*

beta-Lactams, Gunda I. Georg, Ed.; VCH Publishers Inc., New York, N.Y., USA, 1992, pp 1 to 48 and 257 to 293.)

- 5 Compounds of formula 1 wherein R^1 to R^5 , inclusive, and Z are as defined herein can be prepared by a process selected from one of the following processes:

A) reacting a key intermediate of formula 2:



(2)

10

wherein R^1 , R^2 , R^3 and Z are as defined herein either

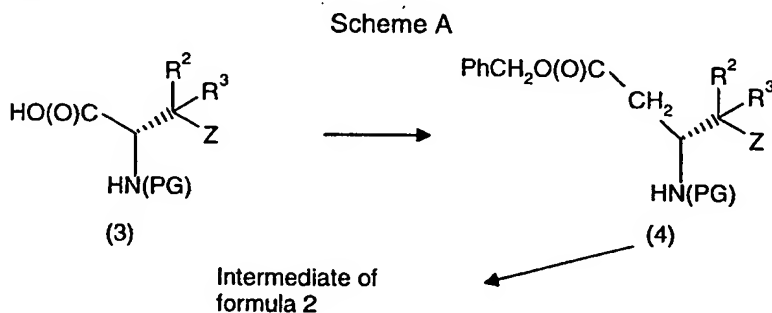
- (a) with an isocyanate of formula R^5NCO wherein R^5 is as defined herein in the presence of a proton acceptor, or (b) with a phoxycarbamate of formula $R^5NHC(O)OPh$ in the presence of a proton acceptor, to obtain the corresponding compound of formula 1 wherein R^1 , R^2 , R^3 , R^5 and Z are as defined herein and R^4 is hydrogen; or

- B) reacting the key intermediate of formula 2 wherein R^1 , R^2 , R^3 and Z are as defined herein with a carbamoyl chloride derivative of formula $R^4R^5NC(O)Cl$ wherein R^4 is lower alkyl, methoxy, ethoxy or benzyloxy, and R^5 is as defined herein, or R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino, N-methylpiperazino, 1-(3,4-dihydro-1H-isoquinolinyl or 2-(3,4-dihydro-1H-isoquinolinyl) in the presence

25

of a proton acceptor to obtain the corresponding compound of formula 1 wherein R^1 , R^2 , R^3 and R^5 are as defined herein, and R^4 is lower alkyl, methoxy, ethoxy or benzyloxy, or R^4 and R^5 together with the nitrogen atom to which they are attached are as defined herein, and Z is as defined herein.

The aforementioned key intermediate of formula 2 can be prepared by a process illustrated by Scheme A as follows:



wherein PG is an amino protecting group and R^2 , R^3 and Z are as defined herein.

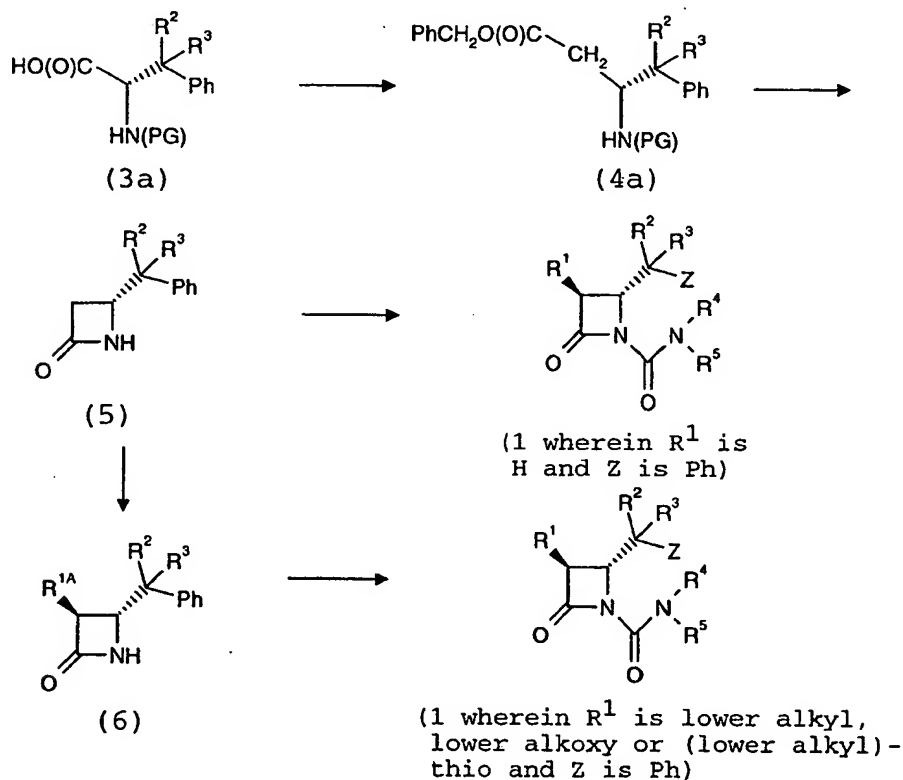
The starting material of formula 3 is either commercially available or can be made by known methods.

With reference to Scheme A, the protected amino acid (3) is homologized by well known procedures to give the benzyl ester of the corresponding β -amino acid (4). The latter benzyl ester is deprotected to provide the corresponding free amino acid which is cyclodehydrated according to known procedures, see for instance M.F. Loewe et al., Tetrahedron Letters **1991**, 32, 2299; and S. Kobayashi et al., J. Am. Chem.

Soc., 1981, 103, 2406, to give the key intermediate of formula 2.

The preparation of the compound of formula 1 can be illustrated further by reference to scheme B wherein PG, R², R³ and R⁵ are as defined herein and R¹, R^{1a} and R⁴ are as defined hereinbelow in the description of scheme B.

Scheme B



With reference to Scheme B, commercially available, suitably protected amino acid (3a) is homologized by standard procedures to give the benzyl ester of the corresponding β -amino acid (4a). The latter benzyl ester is deprotected to provide the corresponding free amino acid which is cyclodehydrated by known procedures to give a key intermediate of formula 5.

Condensation of the key intermediate (5) with an appropriate isocyanate of formula R^5NCO in the presence of a proton acceptor affords a corresponding ureido derivative which is the compound of formula 1 wherein R^1 , R^4 are hydrogen and R^2 , R^3 and R^5 inclusive are as defined herein. Alternatively, a primary or secondary amine, or salts thereof, can be preactivated with triphosgene in presence of a base, for example diisopropylethylamine; or via the formation of the phenoxycarbamate derivative which in turn is reacted with the intermediate of formula 5; to provide the preceding compound of formula 1 wherein R^1 is hydrogen.

Optionally, the key intermediate of formula 5 can be functionalized at position 3 of the azetidin-2-one ring; namely, the nitrogen atom of the intermediate of formula 5 is first protected with a suitable N-protecting group and then the resulting N-protected derivative is alkylated by standard methods at position 3. Subsequent deprotection gives the functionalized intermediate (6). Intermediate (6) thereafter can be transformed to the desired ureido compound of formula 1 wherein R^1 is lower alkyl, lower alkoxy or (lower alkyl)thio in the same manner as described above for the transformation of key intermediate (5) to the ureido compound of formula 1 wherein R^1 is hydrogen and R^2 to R^5 , inclusive, are as defined herein.

The process of this invention can be illustrated further by more specific reference to the process depicted by Scheme B.

Accordingly, an amino protected phenylalanine derivative of formula 3a is homologized to the benzyl ester (4a) according to the following procedure:

- 5
- (a) reacting an amino protected phenylalanine derivative of formula 3a wherein PG is an amino protecting group and R^2 and R^3 are as defined herein in the presence of alkyl chloroformate, preferably
- 10 isobutyl chloroformate, and a tertiary organic base, e.g. N-methylmorpholine or triethylamine, to obtain a corresponding mixed anhydride, (b) reacting the mixed anhydride with diazomethane to obtain a corresponding diazomethylketone, and (c) rearranging the
- 15 diazomethylketone with silver benzoate in the presence of benzyl alcohol and a tertiary organic base, e.g. N-methylmorpholine or triethylamine, to obtain a corresponding benzyl ester (4a).
- 20 Thereafter, benzyl ester (4a) is subjected to deprotection conditions, for instance hydrogenation in the presence of a catalytic amount of palladium hydroxide on carbon when PG is a benzyloxycarbonyl protecting group, to give the corresponding β -amino
- 25 acid. The latter compound is subjected to cyclodehydration conditions, for instance methanesulfonyl chloride/sodium bicarbonate, in a suitable solvent, e.g. acetonitrile, to give the key intermediate of formula 5 in which R^2 and R^3 are as
- 30 defined herein.

The key intermediate of formula 5 can be transformed to the azetidinone derivative of formula 1 wherein R^1 and R^4 each is hydrogen, R^2 , R^3 , R^5 are as defined

herein and Z is phenyl by reacting the key intermediate of formula 5 with an appropriate isocyanate of formula R^5NCO wherein R^5 is as defined herein in the presence of a base (proton acceptor.)

5 A convenient and practical base is triethylamine or preferably lithium bis(trimethylsilyl)amide. In this manner the ureido residue is incorporated into the desired azetidinone (i.e. the compound of formula 1 wherein R^1 and R^4 each is hydrogen, R^2 , R^3 and R^5 are

10 as defined herein and Z is phenyl).

A method for the introduction of the ureido residue so that azetidinone derivatives of formula 1 can be realized for those derivatives in which R^1 is

15 hydrogen, R^2 , R^3 and R^5 are as defined herein, R^4 is lower alkyl, methoxy, ethoxy or benzyloxy, or R^4 and R^5 together with the nitrogen atom to which they are attached are as defined herein, and Z is phenyl is as follows: reacting the key intermediate (5) with a

20 carbamoyl chloride derivative of formula $R^4R^5NC(O)Cl$ wherein R^4 is lower alkyl, methoxy, ethoxy or benzyloxy, and R^5 is as defined herein, or R^4 and R^5 together with the nitrogen atom to which they are attached are as defined herein, in the presence of a

25 suitable tertiary amine, for example diisopropylethylamine or preferably lithium bis(trimethylsilyl)amide. The requisite carbamoyl chloride derivative can be prepared by preactivating the appropriate secondary amine with triphosgene. This

30 particular method for the formation of the ureido residue is especially suitable for the preparation of azetidinone derivatives in which R^4 is lower alkyl,

and for the preparation of azetidinone derivatives in which R^4 and R^5 together with the nitrogen atom to which they are attached are as defined herein.

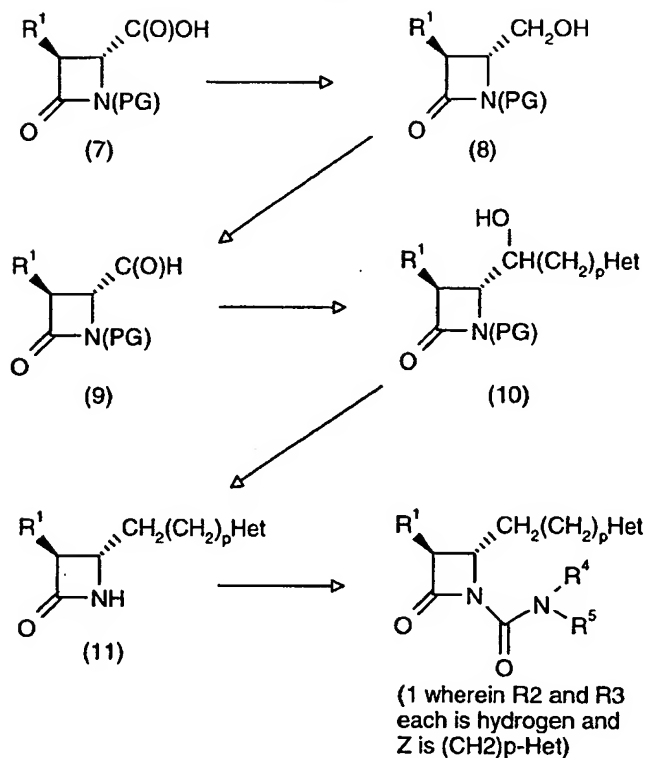
- 5 Another method for forming the ureido residue to obtain the desired azetidinone derivatives of formula 1 is which R^1 and R^4 each is hydrogen, R^2 , R^3 and R^5 are as defined herein and Z is phenyl involves reacting the key intermediate (5) with a
- 10 phenoxycarbamate of formula $R^5HNC(O)OPh$ wherein R^5 is as defined herein in the presence of a suitable base (proton acceptor), e.g. triethylamine or preferably lithium bis(trimethylsilyl)amide, thereby obtaining the desired product.

- 15 Turning now to the preparation of the azetidinones of formula 1 in which R^1 is methyl, ethyl, methoxy or methylthio, R^2 to R^5 , inclusive, are as defined herein and Z is phenyl, the versatile intermediate of
- 20 formula 5 can be functionalized at position 3 of the azetidinone ring as follows: Firstly a N-protecting group, such as benzyl, (4-methoxyphenyl)methyl or preferably tert-butyldimethylsilyl ($Me_3C-Si(Me)_2-$), is introduced at position 1 of the intermediate (5).
- 25 The resulting amino protected derivative of formula 5 then is subjected to standard alkylating conditions with the appropriate electrophilic reagent. More explicitly, enolate formation is effected in the presence of a suitable proton acceptor, e.g. lithium
- 30 diisopropylamide or lithium bis(trimethylsilyl)amide. Thereafter, the enolate is reacted with (a) a methyl or ethyl halide, e.g. methyl iodide or ethyl iodide; or b) with oxygen in the presence of

- trimethylphosphite to provide the corresponding 3-hydroxy substituted, which in turn is reacted with diazomethane in the presence of silica gel; or c) with dimethyldisulfide; followed by N-deprotection
- 5 under standard conditions to give the corresponding functionalized intermediate of formula 6 wherein R^1 is methyl or ethyl, or methoxy, or methylthio, respectively, and R^2 and R^3 are as defined herein.
- 10 Thereafter, the functionalized intermediate of formula 6 is converted to the desired compound of formula 1 wherein R^1 is methyl, ethyl, methoxy or methylthio, R^2 to R^5 , inclusive, are as defined herein and Z is phenyl in the same manner as
- 15 described above for the introduction of the ureido residue in the transformation of the key intermediate of formula 5 to the compound of formula 1 in which R^1 is hydrogen, R^2 to R^5 , inclusive, are as defined herein and Z is phenyl.
- 20 Finally, the preparation the azetidinones of formula 1 wherein R^2 and R^3 each is hydrogen, R^1 , R^4 , R^5 are as defined herein and Z is $(CH_2)_p$ -(Het) wherein p and Het are as defined herein can be illustrated by
- 25 Scheme C wherein PG, R^1 , R^4 , R^5 , Het and p are as defined herein:

23

Scheme C



With reference to Scheme C, suitably N-protected 4-carboxyazetidinones of formula 7 wherein R¹ is as defined herein and PG is an amino protecting group are well known or can be prepared by known methods such as the methods for functionalizing position 3 of azetidinones described hereinbefore. For example, the N-protected 4-carboxyazetidinone of formula 7 wherein PG is the protecting group Me₃CSi(Me)₂- has been described by P.E. Finke et al., *J. Med. Chem.* **1995**, *38*, 2449. The N-protected 4-carboxyazetidinone of formula 7 is reduced to the corresponding 4-(hydroxymethyl)azetidinone derivative of formula 8 with a reducing agent capable of converting an acid to its corresponding alcohol. The 4-(hydroxymethyl)azetidinone is then oxidized to give the aldehyde of formula 9 with a reagent capable of

transforming a primary alcohol to its corresponding aldehyde. The latter aldehyde so obtained is reacted with an appropriate Grignard reagent of the formula $\text{Het}(\text{CH}_2)_p\text{-(halo)Mg}$ wherein Het and p are as defined
5 herein and halo is bromo, chloro or iodo, or with an appropriate organolithium reagent of the formula $\text{Het}(\text{CH}_2)_p\text{-Li}$ to give the product (10). Subsequent removal of the secondary hydroxy group on the side chain at position 4 of product (10) by standard
10 methods, for instance by conversion of the hydroxy moiety to a reducible group which is subsequently removed by reduction, followed by cleavage of the N-protecting group from the resulting protected β -lactam affords the desired intermediate β -lactam of
15 formula 11.

More explicitly, the transformation of the 4-carboxyazetidinone (7) to the desired intermediate (11) can be exemplified as follows: Reduction of the
20 4-carboxyazetidinone (7) wherein PG is $\text{Me}_3\text{CSiMe}_2\text{-}$ and R^1 is as defined herein with borane in tetrahydrofuran, or via the formation of a mixed anhydride with isobutyl chloroformate in the presence of an organic tertiary base, e.g. N-methylmorpholine
25 or diisopropylethylamine, followed by reduction of the mixed anhydride with sodium borohydride in water, yields the 4-(hydroxymethyl)azetidinone (8) wherein PG is $\text{Me}_3\text{CSiMe}_2\text{-}$ and R^1 is as defined herein. The latter compound is oxidized with an appropriate
30 oxidizing agent, e.g. oxalyl chloride-activated dimethyl sulfoxide (K. Omura and D. Swern, *Tetrahedron* **1978**, 34, 1651) or triacetoxy periodinane (D.B. Dess and J.C. Martin, *J. Org. Chem.* **1983**, 48,

4155) to give the corresponding aldehyde of formula 9. This aldehyde subsequently is reacted with the appropriate Grignard reagent $\text{Het}(\text{CH}_2)_p\text{-Mg-(halo)}$ as defined hereinbefore, or with the organolithium reagent $\text{Het}(\text{CH}_2)_p\text{-Li}$ as defined hereinbefore to give the addition product (10) as a mixture of diastereoisomers. Deoxygenation of the hydroxy-bearing side chain of addition product (10) can be accomplished in two steps. Firstly, the corresponding diastereoisomeric xanthates can be formed by reacting product (10) with carbon disulfide in the presence of a tertiary amine or with 1,1'-thiocarbonyldiimidazole; the diastereoisomeric xanthates so obtained are reacted with tributyltin hydride in the presence of 2,2'-azobisisobutyronitrile (AIBN) in refluxing benzene. In this manner, deoxygenation of the hydroxy bearing side chain is effected, followed by removal of the N-protecting group to provide the desired intermediate β -lactam of formula 11. The latter intermediate can be transformed into a compound of formula 1 wherein R^2 and R^3 each is hydrogen, R^1 , R^4 and R^5 are as defined herein, and Z is $(\text{CH}_2)_p\text{-Het}$ wherein p and Het are as defined herein in the same manner as described above for the introduction of the ureido residue to the intermediate of formula 5.

More specifically when Het is a tetrazol derivative, intermediate (11) was obtained from derivative (8) using published procedures (J. Fetter; E. Keskeny; T. Czuppon; K. Lempert; M. Kajtar-Peredy; J. Tamas. *J. Chem. Soc. Perkin Trans. 1992*, 1, 3061-3067 and L.T. Giang; J. Fetter; K. Lempert; M. Kajtar-Peredy; A. Gomory; *Tetrahedron*, 1996, 52, 10169-10184).

Antiherpes Activity

The antiherpes activity of the aforementioned
5 azetidinone derivatives of formula 1 (HCMV protease
inhibitors) can be demonstrated by biochemical,
microbiological and biological procedures.

A biochemical procedure for demonstrating anti-
10 cytomegalovirus activity for the azetidinone
derivatives of formula 1 is described in the examples
hereinafter. This particular assay determines the
ability of a test compound to inhibit the activity of
HCMV protease. More specifically, in the assay
15 described herein, the inhibitory activity of the test
compound is evaluated on the basis of its ability to
interfere with the HCMV N₀ protease cleavage of a
fluorogenic peptide substrate which in turn is based
on the maturation cleavage site of the enzyme.

20
Methods for demonstrating the inhibiting effect of
the azetidinone derivatives of formula 1 on CMV
replication involving cell culture techniques are
described in the examples herein.

25
When the HCMV protease inhibitor is employed as an
antiviral agent, it is administered orally, or
systemically to humans in a vehicle comprising one or
more pharmaceutically acceptable carriers, the
30 proportion of which is determined by the solubility
and chemical nature of the compound, chosen route of
administration and standard biological practice. For
oral administration, the compound or a
therapeutically acceptable salt thereof can be
35 formulated in unit dosage forms such as capsules or

tablets each containing a predetermined amount of the active ingredient, ranging from about 50 to 500 mg, in a pharmaceutically acceptable carrier.

- 5 For parenteral administration, the HCMV protease inhibitor is administered by either intravenous, subcutaneous or intramuscular injection, in compositions with pharmaceutically acceptable vehicles or carriers. For administration by
- 10 injection, it is preferred to use the compounds in solution in a sterile aqueous vehicle which may also contain other solutes such as buffers or preservatives as well as sufficient quantities of pharmaceutically acceptable salts or of glucose to
- 15 make the solution isotonic.

Suitable vehicles or carriers for the above noted formulations are described in standard pharmaceutical texts, e.g. in "Remington's The Science and Practice

20 of Pharmacy", 19th ed., Mack Publishing Company, Easton, Penn., 1995, or in "Pharmaceutical Dosage Forms and Drug Delivery Systems", 6th ed., H.C. Ansel et al., Eds., Williams & Wilkins, Baltimore, Maryland, 1995.

- 25
- The dosage of the HCMV protease inhibitor will vary with the form of administration and the particular active agent chosen. Furthermore, it will vary with the particular host under treatment. Generally,
- 30 treatment is initiated with small increments until the optimum effect under the circumstance is reached. The inhibitor compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any
- 35 harmful or deleterious side effects.

For oral administration, the HCMV protease inhibitor is administered in the range of 20 to 200 mg per kilogram of body weight per day, with a preferred
5 range of 25 to 100 mg per kilogram.

For ocular administration, the HCMV protease inhibitor is administered either topically or intraocularly (injection or implant) in a suitable
10 preparation. For example, an implant containing the compound in a suitable formulation can be surgically plated in the posterior segment of the eye through a small incision.

15 With reference to systemic administration, the HCMV protease inhibitor is administered at a dosage of 10 mg to 150 mg per kilogram of body weight per day, although the aforementioned variations will occur. However, a dosage level that is in the range of from
20 about 10 mg to 100 mg per kilogram of body weight per day is most desirably employed in order to achieve effective results.

EXAMPLES

25 The following examples further illustrate this invention. All reactions were performed under nitrogen or argon atmosphere unless stated otherwise. Temperatures are given in degrees Celsius. Solution
30 percentages or ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance spectra were recorded on a Bruker 400 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. Abbreviations or
35 symbols used herein include Abz: 2-aminobenzoic acid;

Bzl: benzyl (also known as phenylmethyl); DIEA: diisopropylethylamine; DMF: dimethylformamide; DMSO: dimethylsulfoxide; EDTA: ethylenediaminetetracetic acid; Et: ethyl; EtOAc: ethyl acetate; Et₂O: diethyl ether; HRMS: high resolution mass spectrometry; MS(ES): electrospray mass spectrometry; MS(FAB) or FAB/MS: fast atom bombardment mass spectrometry; FBS: fetal bovine serum; Me: methyl; MeOH: methanol; MeCN: acetonitrile; PFU: plaque forming units; Ph: phenyl; THF: tetrahydrofuran.

Example 1

4(*S*)-Benzyl-3(*S*)-methyl-2-oxoazetidine-1-carboxylic acid benzylamide (1: R¹ = Me, R², R³ and R⁴ each = H, R⁵ = Bzl and Z = Ph) (Table 2, entry #207).

Step A

To a solution of N-(benzyloxycarbonyl-L-phenylalanine (18.7 g, 62 mmol) in THF (300 mL) was added Et₃N (6.9 g, 9.5 mL, 68 mmol). The mixture was cooled to -10°. Isobutylchloroformate (11.0 g, 10.5 mL, 81 mmol) was added dropwise over 10 min. After 30 min at -10°, and 30 min at room temperature (20-22°), a solution of diazomethane in Et₂O (0.3-0.5 M, 500 mL) was added. The reaction mixture was stirred for 10 min and then purged with nitrogen for 2 h. The resulting white precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (SiO₂, 20% EtOAc in hexane) to give 15.9 g (83% yield) of the desired diazoketone as a yellow solid.

30

The diazoketone (13.2 g, 43 mmol) was dissolved in THF (150 mL). Benzyl alcohol (4.66 mL, 45 mmol) was added at room temperature. Silver benzoate (977 mg, 4.29 mmol) in triethylamine (8.92 mL, 64 mmol) was added dropwise (vigorous gas evolution). After 30 min at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc. The solution was washed with H₂O and brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (SiO₂, 15% EtOAc in hexane) to yield 3(*S*)-
5 {{{(benzyloxy)carbonyl}amino}-4-phenylbutyric acid benzyl ester (11 g, 63% yield) as a white solid.
¹H-NMR (400 MHz, CDCl₃) δ 7.40-7.10 (m, 15H), 5.27 (brd, J = 8.0 Hz, 1H), 5.14 (d, J = 12.2 Hz, 1H), 5.10 (d, J' = 12.2 Hz, 1H), 5.06 (s, 2H), 4.30-4.20 (m, 1H), 2.93 (dd, J = 13.3, 6.5 Hz, 1H), 2.82 (dd, J = 13.3, 7.6 Hz, 1H), 2.57 (dd, J = 16, 5.5 Hz, 1H), 2.50 (dd, J = 16, 5.0 Hz, 1H).

20

Step B

The 3(*S*)-{{{(benzyloxy)carbonyl}amino}-4-phenylbutyric acid benzyl ester (from step A) (10.97 g, 27.2 mmol) in MeOH (1 L) was stirred at room temperature for 7 h under an hydrogen atmosphere (1 atmosphere) in the presence of 20% Pd (OH)₂/C (50 mg). The catalyst was removed by filtration through diatomaceous earth. The filtrate was concentrated under reduced pressure to yield 4.53 g (93% yield) of 3(*S*)-amino-4-phenylbutyric acid as a white solid.

30

A suspension of NaHCO₃ (12.74 g, 152 mmol) in MeCN (1.55 L) was stirred and heated to gentle reflux. Mesyl chloride (2.15 mL, 27.8 mmol) was added,

followed by the portionwise addition of the preceding acid (4.53 g, 25.3 mmol) over 5 h. After 16 h under reflux, the solid was removed by filtration at 60° and the filtrate was concentrated under reduced pressure. The residual solid was triturated with EtOAc and filtered. The filtrate was concentrated and the residue purified by flash chromatography (SiO₂, 40% EtOAc in hexane) to give 4(*S*)-benzylazetidin-2-one (2.20 g, 54% yield) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.35-7.17 (m, 5H), 5.83 (brs, 1H), 3.88-3.82 (m, 1H), 3.08 (ddd, J = 14.8, 5.0, 2.2 Hz, 1H), 2.98 (dd, J = 13.7, 5.7 Hz, 1H), 2.84 (dd, J = 13.7, 7.9 Hz, 1H), 2.70 (ddd, J = 14.9, 2.0, 1.3 Hz, 1H).

15

Step C

To a solution of 4(*S*)-benzylazetidin-2-one (400 mg, 2.48 mmol) in CH₂Cl₂ (8 mL) was added DIEA (648 μL, 3.72 mmol), followed by *tert*-butyldimethylsilyl chloride (411 mg, 2.73 mmol). The reaction mixture was stirred for 16 h at room temperature. The CH₂Cl₂ was evaporated and the residue was purified by flash chromatography (SiO₂, 12% EtOAc in hexane) to give 4(*S*)-benzyl-1-(*tert*-butyldimethylsilyl)azetidin-2-one (647 mg, 95% yield) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.34-7.15 (m, 5H), 3.77-3.70 (m, 1H), 3.25 (dd, J = 13.5, 3.5 Hz, 1H), 2.99 (dd, J = 15.5 Hz, 5 Hz, 1H), 2.70 (dd, J = 15.5, 2.5 Hz, 1H), 2.59 (dd, J = 13.5, 11 Hz, 1H), 1.01 (s, 9H), 0.31 (s, 3H), 0.29 (s, 3H).

30

Step D

To a solution of diisopropylamine (705 μ L, 5.03 mmol) in anhydrous THF (12 mL) at -20° was added butyllithium (2.87 mL, 4.60 mmol, 1.6 M in hexane). After the reaction mixture was cooled to -78° , a

5 solution of 4(*S*)-benzyl-1-(*tert*-butyldimethylsilyl)azetidin-2-one (640 mg, 2.32 mmol) in THF (4 mL) was added and the mixture was stirred at -78° for 15 min followed by addition of methyl iodide (488 mg, 214 μ L, 3.44 mmol). After 10 min, the reaction

10 mixture was poured into EtOAc (125 mL). The organic phase was washed with aqueous NaHSO_4 (1M) and brine, dried (MgSO_4), filtered and concentrated. The residual oil was purified by flash chromatography (SiO_2 , 6% EtOAc in hexane) to give 4(*S*)-benzyl-1-

15 (*tert*-butyldimethylsilyl)-3(*S*)-methylazetidin-2-one (557 mg, 83% yield) as a pale yellow solid.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.33-7.15 (m, 5H), 3.35 (ddd, $J = 10.8, 3.8, 2.5$ Hz, 1H), 3.21 (dd, $J = 13.4, 3.8$ Hz, 1H), 2.88 (qd, $J = 7.5, 2.5$ Hz, 1H), 2.60 (dd, $J = 13.4, 10.8$ Hz, 1H), 1.02 (d, $J = 7.5$ Hz, 3H),

20 1.00 (s, 9H), 0.31 (s, 3H), 0.27 (s, 3H).

Step E

To a solution of 4(*S*)-benzyl-1-(*tert*-butyldimethylsilyl)-3(*S*)-methylazetidin-2-one (557 mg, 1.92 mmol) in MeOH (25 mL) at 0° was added cesium fluoride (439 mg, 2.89 mmol). After 1 h MeOH was evaporated under reduced pressure and the residue was dissolved in EtOAc. The organic phase was washed with H₂O and brine, dried (MgSO₄), filtered and concentrated. The residue was purified by flash chromatography (SiO₂, 50% EtOAc in hexane) to give 4(*S*)-benzyl-3(*S*)-methylazetidin-2-one (239 mg, 71% yield) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.35-7.17 (m, 5H), 5.78 (brs, 1H), 3.46 (ddd, *J* = 8.0, 5.9, 2.0 Hz, 1H), 2.98 (dd, *J* = 13.5, 5.9 Hz, 1H), 2.91 (qd, *J* = 7.3, 2.0 Hz, 1H), 2.84 (dd, *J* = 13.5, 8.0 Hz, 1H), 1.26 (d, *J* = 7.3 Hz, 3H).

Step F

To a solution of 4(*S*)-benzyl-3(*S*)-methylazetidin-2-one (50 mg, 0.28 mmol) in THF (4 mL) at -78°, lithium bis(trimethylsilyl)amide (280 µL, 280 mmol, 1 M in THF) was added. After 10 min, benzyl isocyanate (37.2 mg, 34.6 µL, 0.28 mmol) was added. Stirring was continued at -78° for 45 min. The reaction mixture was diluted with EtOAc (50 mL) and washed with aqueous NaHSO₄ (1M) and brine, dried (MgSO₄), filtered and concentrated. The residue was purified by flash chromatography (SiO₂, 14% EtOAc in hexane) to give the title compound 4(*S*)-benzyl-3(*S*)-methyl-2-oxoazetidine-1-carboxylic acid benzylamide (23 mg, 27% yield) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃) δ 7.38-7.19 (m, 10 H), 6.94 (t, J = 5.1 Hz, 1 H), 4.53 (dd, J = 14.9, 6.0 Hz, 1 H), 4.48 (dd, J = 14.9, 6.0 Hz, 1 H), 3.90 (ddd, J = 8.6, 3.2, 2.9 Hz, 1 H), 3.53 (dd, J = 13.7, 3.5 Hz, 1 H), 2.95 (qd, J = 7.6, 2.5 Hz, 1 H), 2.92 (dd, J = 13.3, 8.9 Hz, 1 H), 1.14 (d, J = 7.6 Hz, 3 H); FAB MS m/z 309.3 (MH⁺); HRMS calcd for C₁₉H₂₁N₂O₂: 309.1603 (MH⁺); found: 309.1614.

10

Example 2

4(S)-Benzyl-2-oxoazetidine-1-carboxylic acid benzylamide (1: R¹, R², R³ and R⁴ each = H, R⁵ = Bzl and Z = Ph) (Table 1, entry #116).

15

By following the procedure of step F of example 1, but replacing 4(S)-benzyl-3(S)-methylazetidin-2-one with an equivalent amount of 4(S)-benzylazetidin-2-one, described in step B of example 1, the title compound was obtained.

20

¹H-NMR (400 MHz, CDCl₃) δ 7.46 (t, J = 6.4 Hz, 1H), 7.36-7.21 (m, 10H), 4.36 (d, J = 6.4 Hz, 2H), 4.21 (m, 1H), 3.27 (dd, J = 11.8, 3.8 Hz, 1H), 3.06 (dd, J = 15.8, 5.6 Hz, 1H), 2.93 (dd, J = 11.8, 8.9 Hz, 1H), 2.73 (dd, J = 15.8, 3.0 Hz, 1H); IR (CDCl₃) ν 1769, 1700 cm⁻¹; FAB MS m/z 295.2 (MH⁺); HRMS calcd for C₁₈H₁₉N₂O₂: 295.1447 (MH⁺); found: 295.1452

25

Example 3

1(R)-Phenylpropyl isocyanate (Intermediate for
introducing the 1(R)-phenylpropyl group at R⁵ of the
5 compound of formula 1)

To a solution of 1(R)-phenylpropylamine (14.33 g, 106
mmol) in Et₂O (102 mL) was added a 1.0 M solution of
HCl /Et₂O (212 mL, 212 mmol). The resulting solution
10 was stirred for 30 min and then evaporated to dryness
on a rotary evaporator. The resulting white
hydrochloride salt was suspended in toluene (200 mL).
Triphosgene was added (11.67 g, 39.3 mmol) and the
resulting suspension was stirred at reflux for 3 h
15 and at room temperature for 18 h. The reaction
mixture was concentrated and the final volume
adjusted to 200 mL with toluene giving a final
concentration of 0.53M. The resulting isocyanate
solution was used as such.

20 An aliquot (170 mL) was concentrated to give a
colorless oil:

¹H-NMR (400 MHz, CDCl₃) δ 7.36-7.22 (m, 5H), 4.50 (t,
J = 6.7 Hz, 1H), 1.82 (q, J = 7.3 Hz, 2H), 0.94 (t, J
= 7.3 Hz, 2H).

25

Example 4

4-(((Phenoxycarbonyl)amino)methyl)pyridine
(Intermediate for introducing the 4-(aminomethyl)-
30 pyridinyl group at R⁵ of the compound of formula 1)

To a solution of 4-(aminomethyl)pyridine (10.7 g,
98.5 mmol) in CH₂Cl₂ (245 mL) at 0°, was added Et₃N
(14.2 mL, 19.9 g, 197 mmol), followed by a dropwise

addition of phenylchloroformate (14.8 mL, 18.5 g, 118 mmol). After stirring for 1 h, the resulting mixture was diluted with EtOAc (1.5 L). The organic phase was washed twice with water, then brine, dried over sodium sulfate and concentrated under reduced pressure. Purification of the residue by chromatography (SiO₂, gradient EtOAc to 10 % MeOH / CHCl₃) gave a yellow solid which was recrystallized from EtOAc : hexane (2 : 1) to yield the desired compound (9.55 g, 41.85 mmol, 42 % yield).
¹H-NMR (400 MHz, CDCl₃) δ 8.61 (d, J = 5.7 Hz; 2H), 7.40-7.15 (m, 7H), 5.61 (bs, 1H), 4.50 (d, J = 6.4 Hz, 2H).

15

Example 5

N-Methyl-N-{{4-(trifluoromethyl)phenyl}methyl}-carbamoyl chloride (Intermediate for introducing methyl at R⁴ and {4-(trifluoromethyl)phenyl}methyl at R⁵ of the compound of formula 1)

To a solution of {4-(trifluoromethyl)phenyl}methyl bromide (20.0 g, 83.7 mmol) in EtOH was added methylamine (100 mL of 40% aqueous solution, 1290 mmol). After 2 h, the reaction was concentrated under reduced pressure. The aqueous phase was separated and extracted with EtOAc (2 x 100 mL). The combined organic phase was washed with 5% aqueous NaHCO₃ solution and then brine, dried over magnesium sulfate, filtered and evaporated to dryness. The resulting residue was dissolved in HCl/dioxane (4N, 100 mL). The solvent was removed under reduced pressure. The resulting solid was triturated with Et₂O and collected by suction filtration to provide

37

N-methyl {4-(trifluoromethyl)phenyl}methylaniline hydrochloride salt (17.0 g, 90% yield) as a white solid.

- The salt was suspended in CH_2Cl_2 (150 mL), and the suspension was cooled at 0° . DIEA (30.2 mL, 173 mmol) was added to the cooled solution, followed by the addition of a phosgene solution in toluene (1.93 M, 55 mL, 105.7 mmol). After 2 h at 0° , the reaction mixture was concentrated and the resulting thick gum was extracted with Et_2O . Evaporation of the Et_2O extract gave a light yellow oil which was purified by flash chromatography (SiO_2 : 10% EtOAc in hexane) to give the title compound as a pale yellow oil (16.0 g, 84% yield).
- $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.59 (m, 2H), 7.33 (m, 2H), 4.72 and 4.58 (2 x s, 2H), 3.04 and 2.97 (2 x s, 3H).

Example 6

- 4(S)-tert-Butyl-2-oxoazetidine-1-carboxylic acid (1(R)-phenylpropyl)amide (1: $\text{R}_1=\text{H}$, $\text{R}_2=\text{R}_3=\text{Z}=\text{Me}$, $\text{R}_4=\text{H}$, $\text{R}_5=1-(\text{R})\text{Ph-Pr}$) (Table 2, entry #215).

- By following the same procedure as in example 1, step A, but using 2(S)-{[(benzyloxycarbonyl)amino]-3,3-dimethylbutanoic acid as the starting material, 3(S)-{[(benzyloxycarbonyl)amino]-4,4-dimethylpentanoic acid benzyl ester is obtained as a colorless oil.

- $^1\text{H-NMR}$ (400MHz, CDCl_3) δ 7.28-7.19 (m, 10H), 5.01-4.93 (m, 4H), 4.80 (d, $J = 10.2$ Hz, 1H), 3.94 (td, $J = 9.9, 3.8$ Hz, 1H), 2.59 (dd, $J = 14.6, 4.1$ Hz, 1H), 2.24 (dd, $J = 14.3, 9.9$ Hz, 1H), 0.85 (s, 9H).

Step B

The 3(*S*)-{(benzyloxycarbonyl)amino}-4,4-dimethyl-pentanoic acid benzyl ester (from step A) (490 mg, 1.33 mmol) in EtOH (13.3 mL) was stirred at room temperature for 16 h under an hydrogen atmosphere (1 atmosphere) in the presence of 20% Pd(OH)₂/C (50 mg). The catalyst was removed by filtration over diatomaceous earth. The filtrate was concentrated under reduced pressure to yield 186 mg (96% yield) of the expected amino acid as a white solid.

To a suspension of the amino acid (169 mg, 1.16 mmol) in MeCN (116 mL) and H₂O (20 drops) was added 2-chloro-1-methylpyridinium iodide (356 mg, 1.39 mmol), followed by Et₃N (405 µL, 2.90 mmol). The resulting yellow suspension was stirred for 6 h at reflux, and then at room temperature for 18 h. The mixture was concentrated to dryness and the residue was purified by flash chromatography (SiO₂, 75% EtOAc in hexane) to yield 4(*S*)-*tert*-butylazetidine-2-one (93 mg, 63% yield) as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 5.83-5.67 (bs, 1H), 3.45 (dd, *J* = 5.1, 2.6 Hz, 1H), 2.85 (ddd, *J* = 14.9, 5.1, 2.5 Hz, 1H), 2.69 (ddd, *J* = 14.9, 2.5, 1.0 Hz, 1H), 0.93 (s, 9H).

Step C

Following the same procedure as in example 1, step F, but using 4(*S*)-*tert*-butylazetidine-2-one as starting material and 1(*R*)-phenylpropyl isocyanate as reactant, 4(*S*)-*tert*-butyl-2-oxoazetidine-1-carboxylic acid (1(*R*)-phenylpropyl)amide was obtained as a waxy solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.35-7.24 (m, 5H), 7.21 (d, *J* = 10.2 Hz, 1H), 4.76 (dd, *J* = 15.3, 7.6 Hz, 1H), 3.91 (dd, *J* = 6.0, 3.9 Hz, 1H), 2.96 (dd, *J* = 16.2, 6.0 Hz, 1H), 2.76 (dd, *J* = 16.2, 3.2 Hz, 1H), 1.91-1.79 (m, 2H), 1.03 (s, 9H), 0.93 (t, *J* = 7.3 Hz, 3H); IR (CHCl₃) ν 3361, 1752, 1693 cm⁻¹; FAB MS *m/z* 289.1 (MH⁺); HRMS calcd for C₁₇H₂₅N₂O₂ : 289.1916 (MH⁺); found: 289.1921.

Example 7

4(*S*)-Benzyl-2-oxoazetidine-1-carboxylic acid *N*-methyl-*N*-{{4-(trifluoromethyl)phenyl}methyl}amide (1: R₁=R₂=R₃=H, R₄=Me, R₅=CH₂(4-CF₃)-Ph, Z=Ph) (Table 1, entry #135).

To a solution of 4(*S*)-benzyl-azetidin-2-one (110 mg, 0.68 mmol) (from example 1, step B) in THF (6 mL) at -50°, potassium bis(trimethylsilyl)amide (1.43 mL, 0.717 mmol, 0.5 M in toluene) was added. After 20 min the reaction mixture was added via cannula to a solution of *N*-methyl-*N*-{{4-(trifluoromethyl)phenyl}carbamoyl chloride (from example 5) (860 mg, 3.4 mmol) in THF (6 mL). The reaction mixture was stirred for 2 h during which time the temperature rose to -20°. The reaction was

then quenched with brine (2 mL) and diluted with EtOAc (25 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated. The residue was purified by flash chromatography (SiO₂, 20% EtOAc in hexane) to give the title compound (102 mg, 40% yield) as a colorless oil.

¹H-NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 7.26-7.10 (m, 5H), 4.80-4.53 (m, 2H), 4.41 (m, 1H), 3.15 (dd, J = 14.8, 3.8 Hz, 1H), 2.85 (s, 3H), 2.84 (m, 2H), 2.65 (dd, J = 14.8, 3.5 Hz, 1H); IR (neat) ν 1778, 1665 cm⁻¹, FAB MS m/z 377 (MH⁺); HRMS calcd for C₂₀H₂₀F₃N₂O₂: 377.1477; found: 377.1488.

Example 8

4(S)-Benzyl-2-oxoazetidine-1-carboxylic acid (4-pyridinylmethyl)amide (1: R₁=R₂=R₃=R₄=H, R₅=CH₂-(4-Py), Z=Ph) (Table 1, entry #136).

Following the same procedure as in example 1, step F, but using 4-((phenoxy carbonyl)amino)methylpyridine (from example 4) as reactant instead of benzyl isocyanate, the title compound is obtained as a white solid.

¹H-NMR (400 MHz, CDCl₃) δ 8.55 (m, 2H), 7.38-7.12 (m, 7H), 7.01 (m, 1H), 4.47 (m, 2H), 4.29 (m, 1H), 3.41 (dd, J = 14.0, 3.0 Hz, 1H), 2.99 (dd, J = 16.2, 5.8 Hz, 1H), 2.93 (dd, J = 14.0, 8.4 Hz, 1H), 2.73 (dd, J = 16.2, 2.9 Hz, 1H); IR (CDCl₃) ν 3357, 1764, 1694

cm^{-1} , FAB MS m/z 296.1 (MH^+); HRMS calcd for $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}_2$
: 296.1399; found: 296.1408.

Example 9

5

4(*S*)-Benzyl-3(*S*)-(methylthio)-2-oxoazetidine-1-carboxylic acid (1(*R*)-phenylpropyl)amide (1: $\text{R}_1=\text{MeS}$, $\text{R}_2=\text{R}_3=\text{R}_4=\text{H}$, $\text{R}_5=1$ (*R*)Ph-Pr, $\text{Z}=\text{Ph}$) (Table 2, entry #209).

- 10 Following the same procedure as in example 1, step D, but replacing methyl iodide with dimethyl disulfide, 4(*S*)-benzyl-1-(*tert*-butyldimethylsilyl)-3(*S*)-(methylthio)azetidin-2-one is obtained.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.36-7.20 (m, 5H), 3.75 (d, $J = 2.6$ Hz, 1H), 3.66 (ddd, $J = 10.5, 3.8, 2.2$ Hz, 1H), 3.29 (dd, $J = 13.7, 3.8$, 1H), 2.67 (dd, $J = 13.7, 10.5$ Hz, 1H), 1.82 (s, 3H), 1.03 (s, 9H), 0.34 (s, 3H), 0.31 (s, 3H).

- 20 Following the deprotection procedure described in example 1, step E, but using 4(*S*)-benzyl-1-(*tert*-butyldimethylsilyl)-3(*S*)-(methylthio)azetidin-2-one as the starting material, followed by urea formation as shown in example 1, step F, but using 1(*R*)-phenylpropyl isocyanate (from example 3) as reactant, the title compound is obtained as a colorless oil.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.38-7.21 (m, 10H), 6.90 (d, $J = 8.6$ Hz, 1H), 4.82 (dd, $J = 15.4, 7.5$ Hz, 1H), 4.13 (ddd, $J = 8.3, 2.5, 2.5$ Hz, 1H), 3.77 (d, $J = 2.5$ Hz, 1H), 3.49 (dd, $J = 14.3, 3.5$ Hz, 1H), 3.08 (dd, $J = 14.3, 8.3$ Hz, 1H), 1.93 (s, 3H), 1.93-1.84 (m, 2H), 0.96 (t, $J = 7.3$ Hz, 3H); IR (CHCl_3) ν 3359, 1763, 1702 cm^{-1} ; FAB MS m/z 369.2 (MH^+); HRMS calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_2\text{S}$: 369.1637 (MH^+); found: 369.1646.

Example 10

4(S)-Benzyl-3(S)-methoxy-2-oxoazetidine-1-carboxylic
5 acid (4-pyridinylmethyl)amide (1: R₁=MeO, R₂=R₃=R₄=H,
R₅=CH₂-(4-Py) (Table 2, entry #210).

To a solution of diisopropylamine (800 µL, 5.7 mmol)
in anhydrous THF (40 mL) at -20° was added butyl-
10 lithium (3.56 mL, 5.7 mmol, 1.6 M in hexane). After
15 min., the reaction was cooled to -78°, and freshly
distilled trimethylphosphite (1.12 mL, 7.6 mmol) was
added followed by a solution of 4(S)-benzyl-1-(tert-
butyldimethylsilyl)azetidin-2-one (from example 1,
15 step C, 1.05 g, 3.8 mmol) in THF (10 mL). A constant
stream of oxygen was introduced and the mixture was
stirred at -78° for 3 h. The reaction mixture was
quenched with saturated aqueous NH₄Cl and extracted
with EtOAc (120 mL). The organic layer was washed
20 with brine, dried (MgSO₄), filtered and concentrated.
The residue was purified by flash chromatography
(SiO₂, 10% EtOAc-hexane to 30% EtOAc in hexane) to
give 4(S)-benzyl-1-(tert-butyldimethylsilyl)-3(S)-
hydroxyazetidin-2-one (671 mg, 60% yield) as a white
25 solid.

¹H-NMR (400 MHz, CDCl₃) δ 7.25-7.21 (m, 5H), 4.51 (d,
J = 2 Hz, 1H), 3.75-3.71 (m, 1H), 3.26 (bs, 1H), 3.20
(dd, J = 14, 3.8 Hz, 1H), 2.66 (dd, J = 14, 11.1 Hz,
1H), 1.00 (s, 9H), 0.30 (d, J = 3.5 Hz, 6H).

30

To a solution of 4(S)-benzyl-1-(tert-butyldimethyl-
silyl)-3(S)-hydroxyazetidin-2-one (150 mg, 0.51 mmol)
in Et₂O (70 mL) at 0° was added silica gel (40 - 60
µm, 9 g). The vigorously stirred mixture was treated

with diazomethane in Et₂O (50 mL, 0.3 - 0.5 M solution). Once the yellow color had almost disappeared after about 15 min, additional diazomethane solution (20 mL) was added. This
5 procedure was repeated several times until no more starting material could be detected on TLC (about 1.5 h). The reaction mixture was stirred for an additional hour at room temperature then filtered and concentrated to give 4(S)-benzyl-1-(tert-butyl-
10 dimethylsilyl)-3(S)-methoxyazetidin-2-one (157 mg, 99 % yield) as a white solid which was pure enough for further manipulation.

¹H-NMR (400 MHz, CDCl₃) δ 7.27-7.20 (m, 5H), 4.16 (d, J = 1.9 Hz, 1H), 3.67 (ddd, J = 11.1, 3.8, 1.9 Hz, 1H), 3.23 (dd, J = 13.5, 3.8 Hz, 1H), 2.94 (s, 3H),
15 2.57 (dd, J = 13.4, 11.1 Hz, 1H), 1.01 (s, 9H), 0.32 (d, J = 6 Hz, 6H).

Following the same procedure as in example 1 step E,
20 but using 4(S)-benzyl-1-(tert-butyldimethylsilyl)-3(S)-methoxyazetidin-2-one as the starting material, 4(S)-benzyl-3(S)-methoxyazetidin-2-one was obtained.

¹H-NMR (400 MHz, CDCl₃) δ 7.36-7.18 (m, 5H), 6.00 (brs, 1H), 4.26 (t, J = 1.9 Hz, 1H), 3.80 (ddd, J =
25 7.8, 6.2, 1.6 Hz, 1H), 3.34 (s, 3H), 2.98 (dd, J = 14, 6.2 Hz, 1H), 2.88 (dd, J = 14, 7.8 Hz, 1H).

Following the same procedure as in example 1 step F, but using 4(S)-benzyl-3(S)-methoxyazetidin-2-one as
30 starting material and 4-((phenoxy carbonyl)amino)-methylpyridine as reactant, 4(S)-benzyl-3(S)-methoxy-2-oxoazetidine-1-carboxylic acid (4-pyridinylmethyl)amide was obtained as a light yellow oil.

¹H-NMR (400 MHz, CDCl₃) δ 8.60 - 7.22 (m, 9H), 7.06 - 7.04 (m, 1H), 4.52 - 4.50 (m, 2H), 4.28 (d, J = 2.2 Hz, 1H), 4.21 - 4.17 (m, 1H), 3.57 (dd, J = 14, 3.5Hz, 1H), 3.15 (s, 3H), 2.93 (dd, J = 14.2, 8.9 Hz, 1H); IR (neat) ν 1773, 1770 cm⁻¹; FAB-MS m/z 329 (MH⁺); HRMS calcd for C₁₈H₂₀N₃O₃: 326.1504 (MH⁺); found: 326.1519.

Example 11

10

4(R)-(2-Thiazolylmethyl)-2-oxoazetidine-1-carboxylic acid N-methyl-N-((4-trifluoromethyl)phenyl)methyl amide (1: R₁=R₂=R₃=H, R₄=Me, R₅=CH₂-(4-CF₃-Ph), Z=2-thioazolyl) (Table 2, entry 218).

15

To a solution of 1-(tert-butyldimethylsilyl)-4-oxoazetidine-2(R)-carboxylic acid (15.0 g, 65.40 mmol) in THF (367 mL) at 0°, was added N-methylmorpholine (7.2 mL, 65.40 mmol) and isobutyl chloroformate (8.5 mL, 65.40 mmol). After stirring for 1.5 h at 0° a solution of NaBH₄ (9.9 g, 261.61 mmol) in H₂O (98 mL) was added portionwise. The reaction was stirred for 45 min, then diluted with EtOAc and quenched with aqueous HCl solution (10%) to pH 5-6. The organic phase was collected and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO₃ and brine, dried (MgSO₄), filtered and concentrated. The residual oil was purified by flash chromatography (SiO₂, eluent : gradient 25% to 50% EtOAc / hexane) to provide 1-(tert-butyldimethylsilyl)-4(R)-(hydroxymethyl)azetidin-2-one (8.46 g, 60% yield) as a white solid. ¹H-NMR (400 MHz, CDCl₃) δ 3.74-3.69

30

(m, 1H), 3.65-3.56 (m, 2H), 3.1-2.98 (m, 1H), 2.81-2.76 (m, 1H), 2.01 (s, 1H), 0.89 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H). FAB MS m/z 216.2 (MH⁺).

- 5 A solution of 1-(*tert*-butyldimethylsilyl)-4(*R*)-(hydroxymethyl)azetidin-2-one (309 mg, 1.44 mmol) and Dess-Martin periodinane (917 mg, 2.16 mmol) in CH₂Cl₂ (15 mL) was stirred at room temperature for 1 h. A 1:1 mixture of 10 % aqueous NaHSO₃ : saturated
- 10 aqueous solution of NaHCO₃ (20 mL) was added and the mixture was stirred vigorously until both layers were clear (15 min). The mixture was then extracted with Et₂O, washed with NaHCO₃ and brine, dried (MgSO₄), filtered and concentrated. The resulting aldehyde
- 15 (263 mg, 85 % yield) was immediately dissolved in THF (5 mL) and added dropwise to a solution of 2-lithiothiazole [prepared by the addition of butyllithium (1.3 mmol, 1.04 mL, 1.25 M) to a solution of thiazole (1.3 mmol, 115 mg) in THF (15
- 20 mL) at -50°]. The resulting solution was stirred at -50° for 45 min then quenched with a saturated aqueous solution of NH₄Cl. The mixture was extracted with EtOAc. The extract was washed with brine, dried (MgSO₄), filtered and concentrated. The resulting
- 25 residue was purified by radial chromatography (40 % EtOAc in hexane) to afford the desired mixture of diastereoisomeric alcohols. ¹H-NMR (400 MHz, CDCl₃) δ 7.73 (d, J = 3.2 Hz, 1H), 7.34 (d, J = 3.2 Hz, 1H), 4.98 (d, J = 6.7 Hz, 1H), 4.20 (brs, 1H), 3.93-3.89
- 30 (m, 1H), 3.01 (dd, J = 15.7, 5.7 Hz, 1H), 2.77 (dd, J = 15.7, 2.8 Hz, 1H), 0.99 (s, 9H), 0.30 (s, 3H), 0.24 (s, 3H).

A solution of the diastereoisomeric alcohols (121 mg, 0.41 mmol) and 1,1'-thiocarbonyldiimidazole (216 mg, 1.22 mmol) in CH_2Cl_2 was stirred at room temperature for two days. The resulting mixture was then

5 evaporated and subjected to flash chromatography (SiO_2 , 40 % EtOAc in hexane) to afford the desired mixture of diastereoisomeric xanthates (127 mg, 77 % yield). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 8.40-8.35 (m, 1H), 7.87-7.84 (m, 1H), 7.66-7.58 (m, 1H), 7.44-7.40 (m,

10 1H), 7.10-7.07 (m, 1H), 6.90-6.85 (m, 1H), 6.90-6.85 (m, 1H), 4.47-4.43 and 4.35-4.33 (2 X m, 1H), 3.22 (dd, $J = 15.8, 5.8$ Hz, 1H), 3.02 (dd, $J = 15.8, 2.7$ Hz, 1H), 0.95 and 0.94 (2 X s, 9H), 0.29, 0.27, 0.26 and 0.25 (4 X s, 6H).

15 The latter mixture was dissolved in benzene (2 mL) together with 2,2'-azobisisobutyronitrile (AIBN, 1 mg). The solution was added to a refluxing solution of Bu_3SnH (0.17 mL, 0.62 mmol) in benzene over a 15

20 min period using a syringe pump. The resulting solution was heated at reflux for 1 h, then cooled to room temperature and the residue subjected to flash chromatography (SiO_2 , 40 % EtOAc in hexane) to afford 4(R)-(2-thiazoylmethyl)-1-(tert-

25 butyldimethylsilyl)azetidin-2-one (45 mg, 51 % yield). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.73 (d, $J = 3.2$ Hz, 1H), 7.25 (d, $J = 3.2$ Hz, 1H), 4.02-3.97 (m, 1H), 3.58 (dd, $J = 14.8, 3.5$ Hz, 1H), 3.19 (dd, $J = 15.6, 5.4$ Hz, 1H), 3.11 (dd, $J = 14.8, 9.9$ Hz, 1H), 2.83

30 (dd, $J = 15.6, 2.5$ Hz, 1H), 1.00 (s, 9H), 0.31 (s, 3H), 0.28 (s, 3H).

By following the same procedure as in example 1 step E for the deprotection followed by the ureido formation as in example 7, the title compound, 4(R)-thiazolylmethyl)-2-oxoazetidine-1-carboxylic acid N-methyl-N-((4-trifluoromethyl)phenyl)methyl) amide, was obtained as a yellow gum. ¹H-NMR (400 MHz, CDCl₃) δ 7.72 (d, J = 3.3 Hz, 1H), 7.62 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 3.3 Hz, 1H), 4.70-4.55 (m, 3H), 3.59 (dd, J = 14.9, 4.2 Hz, 1H), 3.45 (dd, J = 14.9, 6.9 Hz, 1H), 3.10-3.00 (m, 2H), 2.97 (s, 3H); IR (neat) ν 1780, 1669 cm⁻¹; FAB-MS m/z 384.2 (MH⁺); HRMS calcd for C₁₇H₁₆F₃N₃O₂S: 384.0994 (MH⁺); found: 384.1003.

15

Example 12

4(R)-(2-methyl-2H-tetrazol-5-ylmethyl)-2-oxoazetidine-1-carboxylic acid N-methyl-N-((4-trifluoromethyl)phenyl)methyl)amide. R₁=R₂=R₃=H, R₄=Me, R₅=CH₂-(4-CF₃-Ph), Z=2-methyl-2H-tetrazolyl) (table 2, entry 223)

The same procedure as in example 7 was followed, but using 4(R)-(2-methyl-2H-tetrazol-5-ylmethyl)azetidine-2-one (that was obtained using published procedures of J. Fetter; E. Keskeny; T. Czuppon; K. Lempert; M. Kajtar-Peredy; J. Tamas. *J. Chem. Soc. Perkin Trans.* **1992**, 1, 3061-3067 and L.T. Giang; J. Fetter; K. Lempert; M. Kajtar-Peredy; A. Gomory; *Tetrahedron*, **1996**, 52, 10169-10184). After ureido formation the title compound was obtained as a yellow gum.

¹H-NMR (400 MHz, CDCl₃) δ 7.56 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.70-4.44 (m, 3H), 4.21 (s,

3H), 3.40 (dd, $J = 15.0$, 4.1 Hz, 1H), 3.28 (dd, $J = 15.0$, 6.5 Hz, 1H), 3.03 (dd, $J = 16.0$, 6.0 Hz, 1H) 2.90 (s, 3H), 2.83 (dd, $J = 16.0$, 3.7 Hz, 1H); IR (neat) ν 1779, 1669, 1322 cm^{-1} ; FAB MS m/z 383.1 (MH⁺); HRMS calcd for $\text{C}_{16}\text{H}_{18}\text{F}_3\text{N}_6\text{O}_2$: 383.1444; found 383.1452.

Example 13

10 The following two assays (A and B) were used to evaluate anti HCMV activity.

A. HCMV N₀ Protease Assay

Material & Methods: Fluorescence measurements were
15 recorded on a Perkin-Elmer LS-50B spectrofluorimeter equipped with a plate reader accessory. UV measurements were recorded on a Thermomax[®] microplate reader from Molecular Devices Corporation, Menlo Park, CA, USA.

20

HCMV N₀ protease was assayed with an internally quenched fluorogenic substrate based on the maturation cleavage site (Abz-VVNASSRLY(3-NO₂)R-OH, $k_{\text{cat}}/K_M = 260 \text{ M}^{-1}\text{s}^{-1}$). The fluorescence increase upon
25 cleavage of the Ala-Ser amide bond was monitored using excitation $\lambda = 312 \text{ nm}$ (slit 2.5nm) and emission $\lambda = 415 \text{ nm}$ (slit 5nm). A protocol adaptable to a 96-well plate format was designed for the determination of IC₅₀ values of inhibitors. Briefly, HCMV N₀ was
30 incubated for 2 ½ h at 30° in presence of the substrate with a range of sequentially diluted inhibitors concentrations (300 to 0.06 μM depending on the potency of each compound). After this period,

enzymatic hydrolysis of the fluorogenic substrate in the absence of inhibitor led to about a 30% conversion. Quenching was not required before fluorescence measurement since the total scanning time by the plate reader accessory was brief relative to the duration of the reaction. The aqueous incubation buffer contained 50 mM tris(hydroxymethyl)aminomethane.HCl pH 8, 0.5M Na₂SO₄, 50 mM NaCl, 0.1 mM EDTA, 1 mM tris(2-carboxyethyl)phosphine.HCl, 3% v/v DMSO and 0.05% w/v casein. The final concentrations of HCMV N₀ protease (expressed in terms of total monomer concentration) and substrate were 100 nM and 5 µM respectively. IC₅₀ values were obtained through fitting of the inhibition curve to a competitive inhibition model using SAS NLIN procedure. The mode of inhibition was determined by measurements of the initial rates (in cuvettes) at various substrate concentrations in the buffer as described above. The IC₅₀ values listed in the following tables the IC₅₀ were obtained according to this assay.

B. Plaque Reduction Assay (PRA):

Hs-68 cells (ATCC # CRL 1635) were seeded in 12-well plates at 83,000 cells/well in 1 mL of DMEM medium (Gibco Canada Inc.) supplemented with 10% fetal bovine serum (FBS, Gibco Canada Inc.). The plates were incubated for 3 days at 37° to allow the cells to reach 80-90% confluency prior to the assay.

The medium was removed from the cells by aspiration. The cells were then infected with approximately 50 PFU of HCMV (strain AD169, ATCC VR-538) in DMEM

medium supplemented with 5% inactivated FBS (assay medium). (DMEM medium is commercially available and has been described by R. Dulbecco et al., *Virology* **1959**, 8, 396.) The virus was allowed to adsorb to
5 cells for 2 h at 37°. Following viral adsorption, the medium was removed from the wells by aspiration. The cells were then incubated with or without 1 mL of appropriate concentrations of test reagent in assay medium. Occasionally, test compounds were added 24 h
10 post-infection. After 4 days of incubation at 37°, the medium was exchanged with fresh medium containing test compound and 4 days later the cells were fixed with 1% aqueous formaldehyde and stained with a 2% violet solution in 20% ethanol in water. Microscopic
15 plaques were counted using a stereomicroscope. Drug effects were calculated as a percent reduction in the number of plaques in the presence of each drug concentration compared to the number observed in the absence of drug. Ganciclovir was used as a positive
20 control in all experiments.

The EC₅₀ values obtained according to this assay for certain azetidine derivatives of this invention are listed in the following table under the heading EC₅₀.

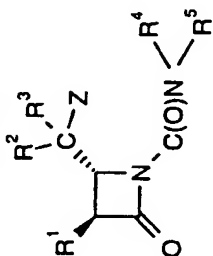
Example 14

In conjunction with the appropriate starting materials and intermediates, the procedures of examples 1 to 11 can be used to prepare other compounds of formula 1. Examples of compounds thus prepared are listed in the following Tables I, II and III together with mass spectrum data for the compounds, and results from the assays A and B of example 12. Cytotoxic effects noted as TC₅₀ in the following tables were determined according to the tetrazolium salt (MTT) metabolic assay, F. Denizot and F. Lang, *J. Immun. Meth.*, **1986**, *89*, 271.

Symbols used in the following tables include 4-AcNH-Ph: 4-(acetylamino)phenyl; 4-NH₂-Ph: 4-aminophenyl; BTZ: benzothiazolyl; Bu: butyl; 4-CF₃-Ph: 4-(trifluoromethyl)phenyl; 4-Cl-Ph: 4-chlorophenyl; 4-COOMe-Ph: 4-(methoxycarbonyl)phenyl; Et: ethyl; 4-F-Ph: 4-fluorophenyl; 4-I-Ph: 4-iodophenyl; 4-isoPr-Ph: 4-(1-methylethyl)phenyl; Me: methyl; 4-MeO-3,5-Me₂-Ph: 4-methoxy-3,5-dimethylphenyl; 4-MeO-Ph: 4-methoxyphenyl; 4-Me-Ph: 4-methylphenyl; 2-NO₂-Ph: 2-nitrophenyl; 4-NO₂-Ph: 4-nitrophenyl; Ph: phenyl; Pr: propyl; 4-Py: 4-pyridinyl; 1-(4-Py)-Pr: 1-(4-pyridinyl)propyl; 4-SCF₃-Ph: 4-((trifluoromethyl)thio)phenyl; 4-SOCF₃-Ph: 4-((trifluoromethyl)sulfinyl)phenyl; 4-SO₂CF₃-Ph: 4-((trifluoromethyl)sulfonyl)phenyl; THZ: thiazolyl.

TABLE I

Compound of formula 1 having the structure

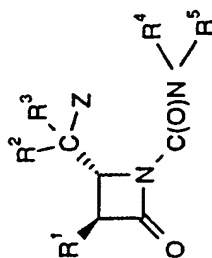


wherein R^1 , R^2 and R^3 each is hydrogen, Z is phenyl and R^4 and R^5 are designated as follows:

Entry No.	R^4	R^5	IC ₅₀ μM	EC ₅₀ μM	TC ₅₀ μM	FAB/MS (MH ⁺)
101	H	4-F-Ph	3.7	>250	>250	299
102	H	4-MeO-Ph	3.9	215	>250	311
103	H	4-Me-Ph	5.3	>250	>250	295
104	H	Ph	3.1	>250	>250	281
105	H	1(R)-(1-naphthalenyl)ethyl	7.7	>18	>18	359
106	H	4-MeO-3,5-Me ₂ -Ph	2.4	190	>250	339
107	H	4-Py	1.9	>250	>250	282
108	H	1(S or R)-(4-Py)-Pr	28			324
109	H	1(R or S)-(4-Py)-Pr	1.6	130	>250	324

TABLE I

Compound of formula 1 having the structure

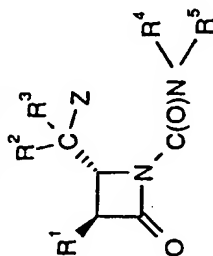


wherein R^1 , R^2 and R^3 each is hydrogen, Z is phenyl and R^4 and R^5 are designated as follows:

Entry No.	R^4	R^5	IC ₅₀ μM	EC ₅₀ μM	TC ₅₀ μM	FAB/MS (MH ⁺)
110	H	Et ₂ CH	38			275
111	H	(5-benzol[1,3]dioxolyl)methyl	3.7	>150	>150	330
112	Me	CH ₂ Ph	10	150	>150	309
113	Me	CH ₃	50			233.1
114	Me	CH ₂ CH ₂ Ph	38			323.2
115	Me	CH ₂ COOCH ₂ Ph	11.7			367
116	H	CH ₂ Ph	8.9	53	>250	295.2
117	Et	CH ₂ Ph	42			323.2
118	H	1(R)-Ph-Pr	2.6	180	>250	323.2
119	Me	1(R)-Ph-Et	24			323

TABLE I

Compound of formula 1 having the structure

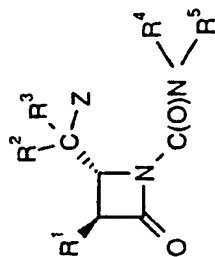


wherein R^1 , R^2 and R^3 each is hydrogen, Z is phenyl and R^4 and R^5 are designated as follows:

Entry No.	R^4	R^5	IC ₅₀ μM	EC ₅₀ μM	TC ₅₀ μM	FAB/MS (MH ⁺)
120	Me	1(S)-Ph-Et	17.7			323
121	H	1(R)-Ph-Bu	3.4	160	>250	337
122	Me	CH ₂ -(4-NO ₂ -Ph)	1.5	105	>250	354.2
123	Me	1(R)-Ph-Pr	30			337.3
124	Me	CH ₂ -(2-NO ₂ -Ph)	6.9	150	>250	354.2
125	Me	CH ₂ -(4-NH ₂ -Ph)	13.4			324.3
126	Me	CH ₂ -(4-Cl-Ph)	6.9	150	>250	343.2
127	H	1(S or R)-(4-Py)-Pr	28			338
128	H	1(R or S)-(4-Py)-Pr	1.6	110	>250	338
129	Me	CH ₂ -(4-Me-Ph)	8.9	140	>200	323.2

TABLE I

Compound of formula 1 having the structure

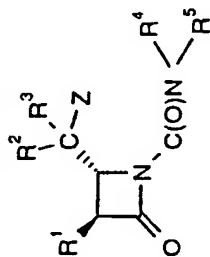


wherein R^1 , R^2 and R^3 each is hydrogen, Z is phenyl and R^4 and R^5 are designated as follows:

Entry No.	R^4	R^5	IC ₅₀ μM	EC ₅₀ μM	TC ₅₀ μM	FAB/MS (MH ⁺)
130	Me	CH ₂ -(4-MeO-Ph)	7.4	110	>250	339.2
131	Me	CH ₂ -(4-COOMe-Ph)	2.5	140	>250	367.2
132	Me	CH ₂ -(4-AcNH-Ph)	17	150	>250	366
133	Me	CH ₂ -(3-NO ₂ -Ph)	6.9	170	>250	354
134	Me	CH ₂ -(4-isoPr-Ph)	6.4	150	200	351
135	Me	CH ₂ -(4-CF ₃ -Ph)	3.7	190	>250	377
136	H	CH ₂ -(4-Py)	13	>250	>250	296.1
137	Me	CH ₂ -(4-SCF ₃ -Ph)	6.9	>250	>250	409
138	Me	CH ₂ -(4-SOCF ₃ -Ph)	8.7	>250	>250	425
139	Me	CH ₂ -(4-SO ₂ CF ₃ -Ph)	4.3	>250	>250	441

TABLE I

Compound of formula 1 having the structure

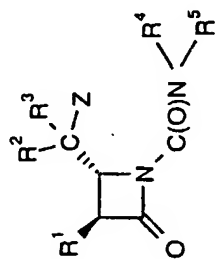


wherein R^1 , R^2 and R^3 each is hydrogen, Z is phenyl and R^4 and R^5 are designated as follows:

Entry No.	R^4	R^5	IC ₅₀ μM	EC ₅₀ μM	TC ₅₀ μM	FAB/MS (MH^+)
140	H		14			321.2
141	H		42			309
142	H		9.7	>250	>250	296

TABLE I

Compound of formula 1 having the structure

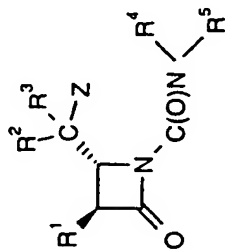


wherein R¹, R² and R³ each is hydrogen, Z is phenyl and R⁴ and R⁵ are designated as follows:

Entry No.	R ⁴	R ⁵	IC ₅₀ μ M	EC ₅₀ μ M	TC ₅₀ μ M	FAB/MS (MH ⁺)
143	H		33			296
144	H	CH ₂ -CH ₂ -Ph	29			309.2
145	Me		6.1	120	>250	334
146	Me		30			268.1

TABLE II

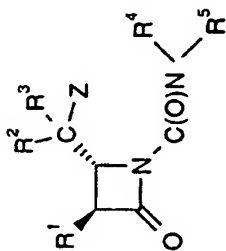
Compounds of formula 1 having the structure

wherein R^1 , R^2 , R^3 , R^4 , R^5 and Z are designated as follows:

Entry No.	R^1	R^2	R^3	R^4	R^5	Z	IC ₅₀ μ M	EC ₅₀ μ M	TC ₅₀ μ M	FAB/MS (MH ⁺)
201	Me	H	H	H	CH ₂ -(4-Py)	Ph	12	190	>250	310
202	Et	H	H	H	CH ₂ -(4-Py)	Ph	58			324.2
203	Me	H	H	H	Ph	Ph	0.81	>250	>250	295.2
204	Me	H	H	H	4-Py	Ph	0.97	205	>250	296.3
205	Me	H	H	H	1(S or R)-(4-Py)-Pr	Ph	21	>250	>250	338
206	Me	H	H	H	1(R or S)-(4-Py)-Pr	Ph	3.2	96	>250	338
207	Me	H	H	H	CH ₂ Ph	Ph	5.3	140	>250	309.3
208	Me	H	H	Me	CH ₂ Ph	Ph	4.2	150	>250	323.3
209	MeS	H	H	H	1(R)-Ph-Pr	Ph	4.7	27	>250	369
210	MeO	H	H	H	CH ₂ -(4-Py)	Ph	2.1	210	>250	326

TABLE II

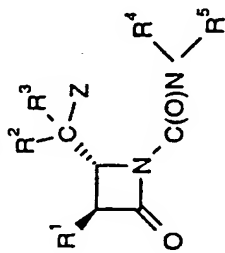
Compounds of formula 1 having the structure

wherein R^1 , R^2 , R^3 , R^4 , R^5 and Z are designated as follows:

Entry No.	R^1	R^2	R^3	R^4	R^5	Z	IC ₅₀ μ M	EC ₅₀ μ M	TC ₅₀ μ M	FAB/MS (MH ⁺)
211	H	H	H	H	CH ₂ -(4-Py)	(4-I-Ph)	8.6	>100	>100	422.1
212	H	H	H	H	1(R)-Ph-Pr	CH ₂ Ph	4.3	140	>250	337.3
213	H	H	Me	H	1(R)-Ph-Pr	Me	5.9	210	>250	275
214	H	H	H	H	1(R)-Ph-Pr	Me	7.6	180	>250	261.1
215	H	Me	Me	H	1(R)-Ph-Pr	Me	41			289.1
216	H	H	Me	H	1(R)-Ph-Pr	(R)-Et	4.4	110	>250	289.1
217	H	H	Me	H	1(R)-Ph-Pr	(S)-Et	11	85	>250	289.1
218	H	H	H	Me	CH ₂ -(4-CF ₃ -Ph)	(2-THZ)	5.5	78	178	384.2
219	H	H	H	Me	CH ₂ -(4-CF ₃ -Ph)	(2-BTZ)	0.88	110	>250	434

TABLE II

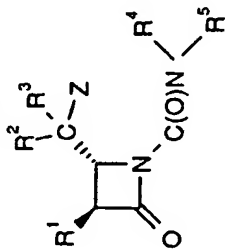
Compounds of formula 1 having the structure

wherein R^1 , R^2 , R^3 , R^4 , R^5 and Z are designated as follows:

Entry No.	R^1	R^2	R^3	R^4	R^5	Z	IC ₅₀ μ M	EC ₅₀ μ M	TC ₅₀ μ M	FAB/MS (MH ⁺)
220	H	H	H	Me			14			444
221	H	H	H	Me			7.1	59	>100	367
222	H	H	H	H			5	125	>148	329

TABLE II

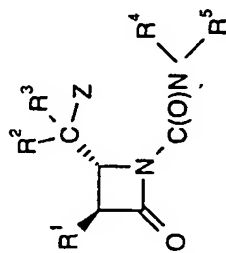
Compounds of formula 1 having the structure

wherein R^1 , R^2 , R^3 , R^4 , R^5 and Z are designated as follows:

Entry No.	R^1	R^2	R^3	R^4	R^5	Z	IC ₅₀ μM	EC ₅₀ μM	TC ₅₀ μM	FAB/MS (MH ⁺)
223	H	H	H	Me			5.7	94	>195	383.1
224	H	H	H	Me			2.7	100	>133	360
225	H	H	H	Me			0.7	30	>50	411
226	H	H	H	Me			1.3	70	>79	360

TABLE II

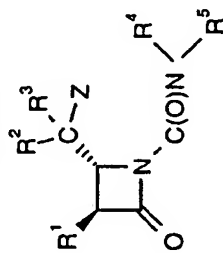
Compounds of formula 1 having the structure

wherein R^1 , R^2 , R^3 , R^4 , R^5 and Z are designated as follows:

Entry No.	R^1	R^2	R^3	R^4	R^5	Z	IC ₅₀ μM	EC ₅₀ μM	TC ₅₀ μM	FAB/MS (MH ⁺)
227	H	H	H	Me			2.5	>29	>29	361
228	H	H	H	Me			4.5	>16	>16	383
229	H	H	H	Me			3.1	143	>261	344.1
230	H	H	H	Me			2.7	11	>25	434

TABLE II

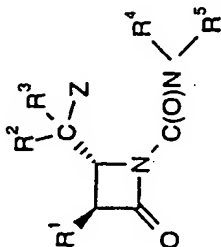
Compounds of formula 1 having the structure

wherein R^1 , R^2 , R^3 , R^4 , R^5 and Z are designated as follows:

Entry No.	R^1	R^2	R^3	R^4	R^5	Z	IC ₅₀ μM	EC ₅₀ μM	TC ₅₀ μM	FAB/MS (MH ⁺)
231	H	H	H	Me			2.7	11	>25	384

TABLE III

Compounds of formula 1 having the structure

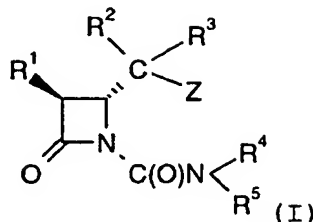


wherein R^1 , R^2 and R^3 each is hydrogen, Z is phenyl, and R^4 and R^5 together with the nitrogen to which they are attached are designated as follows:

Entry No.	$N \begin{smallmatrix} R^4 \\ R^5 \end{smallmatrix}$	IC ₅₀ μM	EC ₅₀ μM	TC ₅₀ μM	FAB/MS (MH ⁺)
301	morpholino	142			275.1
302	2-(3,4-dihydro-1 <i>H</i> -isoquinolinyI)	36			321
303	pyrrolidino	63			259
304	1-(3,4-dihydro-1 <i>H</i> -isoquinolinyI)	154			321.2

Claims:

1. A compound of formula I



- 5 wherein R^1 is hydrogen, methyl, ethyl, methoxy or methylthio;
 R^2 and R^3 each independently is hydrogen or lower alkyl;
 R^4 is hydrogen, lower alkyl, methoxy, ethoxy or
 10 benzyloxy;
 R^5 is lower alkyl, lower cycloalkyl, $(CH_2)_mC(O)OR^6$
 wherein m is the integer 1 or 2 and R^6 is lower
 alkyl or phenyl(lower alkyl);
 phenyl, phenyl monosubstituted, disubstituted or
 15 trisubstituted with a substituent selected
 independently from the group consisting of:
 lower alkyl, lower alkoxy, lower alkylthio,
 halo, hydroxy and amino; phenyl(lower alkyl),
 phenyl(lower alkyl) monosubstituted or
 20 disubstituted on the phenyl portion thereof with
 a substituent selected independently from the
 group consisting of lower alkyl, lower alkoxy,
 lower alkylthio, halo, hydroxy, nitro, amino,
 lower alkylamino, di(lower alkyl)amino, lower
 25 acylamino, di(lower alkyl)aminocarbonyl, cyano,
 trifluoromethyl, (trifluoromethyl)thio,
 (trifluoromethyl)sulfinyl,
 (trifluoromethyl)sulfonyl and $C(O)OR^7$ wherein R^7
 is lower alkyl or phenyl(lower alkyl);

Het or Het(lower alkyl) wherein Het represents an unsubstituted, monosubstituted or disubstituted five or six membered, monovalent heterocyclic ring containing one or two heteroatoms selected from the group consisting of N, O or S, wherein each substituent is selected independently from the group consisting of lower alkyl, lower alkoxy, halo and hydroxy;

5 5-(benzo[1,3]dioxolyl) methyl, (1(R)-1-naphthalenyl)ethyl, 2-benzothiazolyl or 2-thiazolo[4,5-b]pyridinyl; or

10 R^4 and R^5 together with the nitrogen atom to which they are attached form a piperidino, morpholino, thiomorpholino, piperazino, N-methylpiperazino, 1-(3,4-dihydro-1H-isoquinolinyl) or 2-(3,4-dihydro-1H-isoquinolinyl) or a pyrrolidino ring optionally substituted with C(O)Obenzyl or with phenyl said phenyl ring optionally mono- or

15 di-substituted with a substituent selected independently from the group consisting of lower alkyl, lower alkoxy, lower alkylthio, halo, hydroxy, nitro, amino, lower alkylamino, di(lower alkyl)amino, lower acylamino, di(lower alkyl)aminocarbonyl, cyano, trifluoromethyl, (trifluoromethyl)thio,

20 (trifluoromethyl)sulfinyl, (trifluoromethyl)sulfonyl and C(O)OR₇ wherein R₇ is lower alkyl or (lower alkyl)phenyl;

25 and

Z is lower alkyl, phenyl, phenyl monosubstituted or

30 disubstituted with a substituent selected independently from lower alkyl, lower alkoxy, halo, hydroxy and amino; phenylmethyl, phenylmethyl monosubstituted or disubstituted on the phenyl portion thereof with a substituent selected from the group

consisting of lower alkyl, lower alkoxy, halo, -
hydroxy and amino; or $(CH_2)_p$ -(Het) wherein p is the
integer 0 or 1 and Het is as defined herein; with the
proviso that when Z is $(CH_2)_p$ -(Het) as defined herein
5 then R^2 and R^3 each is hydrogen;
or a therapeutically acceptable acid addition salt
thereof.

2. The compound of formula 1 according to claim 1
10 wherein R^1 , R^2 and R^3 are as defined in claim 1;
 R^4 is hydrogen or lower alkyl;
 R^5 is lower alkyl, lower cycloalkyl, $CH_2C(O)OR^6$
wherein R^6 is methyl, ethyl or phenylmethyl;
phenyl, phenyl monosubstituted, disubstituted or
15 trisubstituted with a substituent selected
independently from the group consisting of lower
alkyl, lower alkoxy, lower alkylthio, halo, hydroxy
and amino; phenyl(lower alkyl), phenyl(lower alkyl)
monosubstituted or disubstituted on the phenyl
20 portion thereof with a substituent selected
independently from the group consisting of lower
alkyl, lower alkoxy, lower alkylthio, halo, hydroxy,
nitro, amino, lower alkylamino, di(lower alkyl)amino,
lower acylamino, di(lower alkyl)aminocarbonyl, cyano,
25 trifluoromethyl, (trifluoromethyl)thio,
(trifluoromethyl)sulfinyl, (trifluoromethyl)sulfonyl
and $C(O)OR^7$ wherein R^7 is methyl, ethyl or
phenylmethyl;
Het or Het(lower alkyl) wherein Het is 2-furyl, 2-
30 methyl-3-furyl, 2-thienyl, 2-pyridinyl, 3-pyridinyl,
4-pyridinyl, 3-methyl-2-pyrrolyl, 2-thiazolyl, 4-
thiazolyl, 2-isoxazolyl, 2-pyrimidinyl, 4-methyl-2-
pyrimidinyl, 4,6-dimethyl-2-pyrimidinyl, 4-

pyrimidinyl, 2,6-dimethyl-2-pyrimidinyl, 4-methyltetrazolyl, 2-benzothiazolyl or 2-thiazolo[4,5-b]pyridinyl; (5-benzo[1,3]dioxolyl)methyl, 1(R)-(1-naphthalenyl)ethyl; or

- 5 R^4 and R^5 together with the nitrogen atom to which they are attached form a pyrrolidino, piperidino, morpholino, N-methylpiperazino, 1-(3,4-dihydro-1H-isoquinolinyl) or 2-(3,4-dihydro-1H-isoquinolinyl); and Z is as defined in claim 1.

10

3. The compound of formula 1 according to claim 2 wherein R^1 is hydrogen, methyl, ethyl, methoxy or methylthio;

R^2 and R^3 each independently is hydrogen, or methyl;

- 15 R^4 is hydrogen, methyl, or ethyl;

R^5 is methyl, ethyl, 1-methylethyl, cyclobutyl, cyclopentyl, cyclohexyl, $CH_2C(O)OR^6$ wherein R^6 is methyl or phenylmethyl;

phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,5-

- 20 dimethyl-4-methoxyphenyl, 4-methylphenyl, 4-(methylthio)phenyl, phenylmethyl, phenylethyl, 1-

phenylpropyl, 1-phenylbutyl, phenylmethyl

monosubstituted at position 3 or 4 of the phenyl portion thereof with a substituent selected from the

- 25 group consisting of methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, methoxy, ethoxy,

methylthio, bromo, chloro, fluoro, nitro,

acetylamino, $C(O)NMe_2$, $C(O)NEt_2$, cyano,

trifluoromethyl, (trifluoromethyl)thio,

- 30 (trifluoromethyl)sulfinyl, (trifluoromethyl)sulfonyl

and $C(O)OR^7$ wherein R^7 is methyl, ethyl or

benzyl;

(5-benzo[1,3]dioxolyl)methyl, 1(R)-(1-naphthylenyl)ethyl, 2-pyridinyl, 4-pyridinyl, 2-pyridinylmethyl, 4-pyridinylmethyl, 1-(4-pyridinyl)ethyl or 1-(4-pyridinyl)propyl; or

- 5 R^4 and R^5 together with the nitrogen to which they are attached form a pyrrolidino, piperidino, morpholino, 1-(3,4-dihydro-1*H*-isoquinolinyl) or 2-(3,4-dihydro-1*H*-isoquinolinyl); and Z is phenyl or phenylmethyl.

10

4. The compound of formula 1 according to claim 3 wherein R^1 is hydrogen, methyl or methylthio; R^2 and R^3 each independently is hydrogen or methyl; R^4 is hydrogen, methyl or ethyl;

- 15 R^5 is methyl, ethyl, 1-methylethyl, cyclobutyl, cyclopentyl, cyclohexyl, $CH_2C(O)OR^6$ wherein R^6 is methyl or phenylmethyl;

phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,5-dimethyl-4-methoxyphenyl, 4-methylphenyl, 4-

- 20 (methylthio)phenyl, phenylmethyl, 1-phenylpropyl, 1-phenylbutyl, phenylmethyl monosubstituted at position 3 or 4 of the phenyl portion thereof with a substituent selected from the group consisting of methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, 25 propyl, methoxy, ethoxy, methylthio, bromo, chloro, fluoro, nitro, acetyl amino, $C(O)NMe_2$, $C(O)NEt_2$, cyano, trifluoromethyl, (trifluoromethyl)thio, (trifluoromethyl)sulfinyl, (trifluoromethyl)-sulfonyl and $C(O)OR^7$ wherein R^7 is methyl, ethyl or 30 benzyl;

(5-benzo[1,3]dioxolyl)methyl, 1(R)-(1-naphthalenyl)ethyl, 2-pyridinyl, 4-pyridinyl, 2-

pyridinylmethyl, 4-pyridinylmethyl, 1-(4-pyridinyl)ethyl or 1-(4-pyridinyl)propyl; and **Z** is lower alkyl.

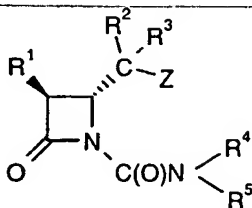
- 5 5. The compound of formula 1 according to claim 4 wherein **R**¹ is hydrogen, methyl, methylthio or methoxy;
R² and **R**³ each independently is hydrogen or methyl;
R⁴ is hydrogen, methyl or ethyl;
- 10 **R**⁵ is methyl, ethyl, 1-methylethyl, cyclobutyl, cyclopentyl, cyclohexyl, CH₂C(O)OR⁶ wherein **R**⁶ is methyl or phenylmethyl;
phenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,5-dimethyl-4-methoxyphenyl, 4-methylphenyl, 4-
- 15 (methylthio)phenyl, phenylmethyl, 1-phenylpropyl, 1-phenylbutyl, phenylmethyl monosubstituted at position 3 or 4 of the phenyl portion thereof with a substituent selected from the group consisting of methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl,
- 20 propyl, methoxy, ethoxy, methylthio, bromo, chloro, fluoro, nitro, acetylamino, C(O)NMe₂, C(O)NEt₂, cyano, trifluoromethyl, (trifluoromethyl)thio, (trifluoromethyl)sulfinyl, (trifluoromethyl)sulfonyl and C(O)OR⁷ wherein **R**⁷ is methyl, ethyl or
- 25 benzyl;
(5-benzo[1,3]dioxolyl)methyl, 1(R)-(1-naphthalenyl)ethyl, 2-pyridinyl, 4-pyridinyl, 2-pyridinylmethyl, 4-pyridinylmethyl, 1-(4-pyridinyl)ethyl or 1-(4-pyridinyl)propyl; and
- 30 **Z** is 2-furyl, 2-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 3-methyl-2-pyrrolyl, 2-thiazolyl, 2-isoxazolyl, 2-pyrimidinyl, 4,6-dimethyl-2-pyrimidinyl, 5-(1-methyl-1H-tetrazolyl), 5-(2-methyl-

2H-tetrazolyl), 2-benzothiazolyl or 2-thiazolo[4,5-b]pyridinyl.

6. The compound of formula 1 according to claim 5
5 wherein R^1 is hydrogen, methyl, methoxy or methylthio;
 R^2 and R^3 each is hydrogen;
 R^4 is hydrogen or methyl;
 R^5 is $CH_2C(O)OR^6$ wherein R^6 is phenylmethyl; or
10 R^5 is 4-fluorophenyl, 4-methoxyphenyl, 3,5-dimethyl-4-methoxyphenyl, (4-methylthio)phenyl, phenylmethyl, 1(R)-phenylethyl, 1(S)-phenylethyl, 1(R)-phenylpropyl, 1(R)-phenylbutyl, (4-methylphenyl)methyl, (4-(1-methylethyl)phenyl)methyl,
15 (4-methoxyphenyl)methyl, (4-chlorophenyl)methyl, (2-nitrophenyl)methyl, (3-nitrophenyl)methyl, (4-(acetylamino)phenyl)methyl, (4-(trifluoromethyl)phenyl)methyl, (4-((trifluoromethyl)thio)phenyl)methyl, (4-((trifluoromethyl)sulfinyl)phenyl)methyl, (4-((trifluoromethyl)sulfonyl)phenyl)methyl, (4-(methoxycarbonyl)phenyl)methyl, (5-benzo[1,3]dioxolyl)methyl, 1(R)-(1-naphthalenyl)ethyl, 4-pyridinyl, 4-pyridinylmethyl or 1-(4-pyridinyl)propyl; or
25 R^4 and R^5 together with the nitrogen to which they are attached form a pyrrolidino, morpholino, 1-(3,4-dihydro-1H-isoquinolinyl) or 2-(3,4-dihydro-1H-isoquinolinyl); and
30 Z is phenyl or phenylmethyl.

7. The compound of formula 1 according to claim 1 selected from the group consisting of:

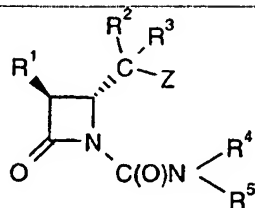
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wherein R^1 , R^2 and R^3 each is hydrogen, Z is phenyl and R^4 and R^5 are designated as follows:

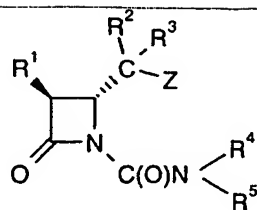
Entry No.	R^4	R^5
101	H	4-F-Ph
102	H	4-MeO-Ph
103	H	4-Me-Ph
104	H	Ph
105	H	1(<i>R</i>)-(1-naphthalenyl)ethyl
106	H	4-MeO-3,5-Me ₂ -Ph
107	H	4-Py
108	H	1(<i>S</i> or <i>R</i>)-(4-Py)-Pr
109	H	1(<i>R</i> or <i>S</i>)-(4-Py)-Pr
110	H	Et ₂ CH
111	H	(5-benzo[1,3]dioxolyl)methyl
112	Me	CH ₂ Ph
113	Me	CH ₃
114	Me	CH ₂ CH ₂ Ph
115	Me	CH ₂ COOCH ₂ Ph
116	H	CH ₂ -Ph
117	Et	CH ₂ -Ph
118	H	1(<i>R</i>)-Ph-Pr
119	Me	1(<i>R</i>)-Ph-Et
120	Me	1(<i>S</i>)-Ph-Et
121	H	1(<i>R</i>)-Ph-Bu
122	Me	CH ₂ -(4-NO ₂ -Ph)
123	Me	1(<i>R</i>)-Ph-Pr
124	Me	CH ₂ -(2-NO ₂ -Ph)
125	Me	CH ₂ -(4-NH ₂ -Ph)

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wherein R^1 , R^2 and R^3 each is hydrogen, Z is phenyl and R^4 and R^5 are designated as follows:

Entry No.	R^4	R^5
126	Me	$\text{CH}_2\text{-(4-Cl-Ph)}$
127	H	1(<i>S</i> or <i>R</i>)-(4-Py)-Pr
128	H	1(<i>R</i> or <i>S</i>)-(4-Py)-Pr
129	Me	$\text{CH}_2\text{-(4-Me-Ph)}$
130	Me	$\text{CH}_2\text{-(4-MeO-Ph)}$
131	Me	$\text{CH}_2\text{-(4-COOMe-Ph)}$
132	Me	$\text{CH}_2\text{-(4-AcNH-Ph)}$
133	Me	$\text{CH}_2\text{-(3-NO}_2\text{-Ph)}$
134	Me	$\text{CH}_2\text{-(4-isoPr-Ph)}$
135	Me	$\text{CH}_2\text{-(4-CF}_3\text{-Ph)}$
136	H	$\text{CH}_2\text{-(4-Py)}$
137	Me	$\text{CH}_2\text{-(4-SCF}_3\text{-Ph)}$
138	Me	$\text{CH}_2\text{-(4-SOCF}_3\text{-Ph)}$
139	Me	$\text{CH}_2\text{-(4-SO}_2\text{CF}_3\text{-Ph)}$
140	H	
141	H	
142	H	
143	H	

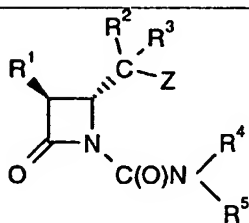


wherein R^1 , R^2 and R^3 each is hydrogen, Z is phenyl and R^4 and R^5 are designated as follows:

Entry No.	R^4	R^5
144	H	CH_2-CH_2-Ph
145	Me	
146	Me	

8. The compound according to claim 7, selected from the group consisting of entries #: 101, 102, 103, 104, 106, 107, 109, 111, 117, 118, 121, 122, 128, 131, 135, and 139.

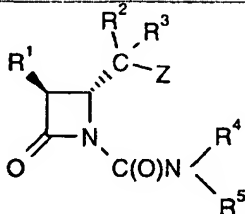
9. The compound of formula 1 according to claim 1 selected from the group consisting of:



wherein R^1 , R^2 , R^3 , R^4 , R^5 and Z are designated as follows:

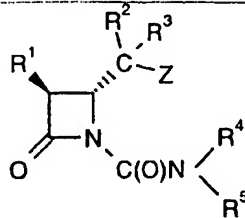
Entry No.	R^1	R^2	R^3	R^4	R^5	Z
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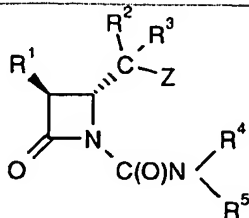
wherein R^1 , R^2 , R^3 , R^4 , R^5 and Z are designated as follows:

Entry No.	R^1	R^2	R^3	R^4	R^5	Z
201	Me	H	H	H	CH_2 -(4-Py)	Ph
202	Et	H	H	H	CH_2 -(4-Py)	Ph
203	Me	H	H	H	Ph	Ph
204	Me	H	H	H	4-Py	Ph
205	Me	H	H	H	1(S or R)-(4-Py)-Pr	Ph
206	Me	H	H	H	1(R or S)-(4-Py)-Pr	Ph
207	Me	H	H	H	CH_2 Ph	Ph
208	Me	H	H	Me	CH_2 Ph	Ph
209	MeS	H	H	H	1(R)-Ph-Pr	Ph
210	MeO	H	H	H	CH_2 -(4-Py)	Ph
211	H	H	H	H	CH_2 -(4-Py)	(4-I-Ph)
212	H	H	H	H	1(R)-Ph-Pr	CH_2 Ph
213	H	H	Me	H	1(R)-Ph-Pr	Me
214	H	H	H	H	1(R)-Ph-Pr	Me
215	H	Me	Me	H	1(R)-Ph-Pr	Me
216	H	H	Me	H	1(R)-Ph-Pr	(R)-Et
217	H	H	Me	H	1(R)-Ph-Pr	(S)-Et
218	H	H	H	Me	CH_2 -(4- CF_3 -Ph)	(2-THZ)
219	H	H	H	Me	CH_2 -(4- CF_3 -Ph)	(2-BTZ)
220	H	H	H	Me		
221	H	H	H	Me		



wherein R^1 , R^2 , R^3 , R^4 , R^5 and Z are designated as follows:

Entry No.	R^1	R^2	R^3	R^4	R^5	Z
222	H	H	H	H		
223	H	H	H	Me		
224	H	H	H	Me		
225	H	H	H	Me		
226	H	H	H	Me		
227	H	H	H	Me		
228	H	H	H	Me		
229	H	H	H	Me		
230	H	H	H	Me		



wherein R^1 , R^2 , R^3 , R^4 , R^5 and Z are designated as follows:

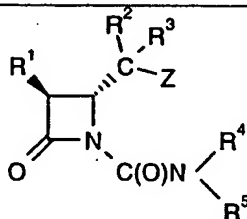
Entry No.	R^1	R^2	R^3	R^4	R^5	Z
231	H	H	H	Me		

10. The compound according to claim 9 selected from the group consisting of entries #: 203, 204, 206, 208, 209, 210, 212, 216, 219, 222, 224, 225, 226, 227, 228, 229, 230, and 231.

11. The compound according to claim 10 selected from the group consisting of entries #: 203, 204, 219, 225 and 226.

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12. The compound according to claim 1 selected from the group consisting of:



wherein R^1 , R^2 and R^3 each is hydrogen, Z is phenyl, and R^4 and R^5 together with the nitrogen to which they are attached are designated as follows

Entry No.	$\begin{array}{c} R^4 \\ \diagdown \\ N \\ \diagup \\ R^5 \end{array}$
301	morpholino
302	2-(3,4-dihydro-1 <i>H</i> -isoquinoliny)
303	pyrrolidino
304	1-(3,4-dihydro-1 <i>H</i> -isoquinoliny)

13. A pharmaceutical composition for treating cytomegalovirus infections in a mammal, including human, comprising a compound of formula 1 according to claim 1, or a therapeutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
14. A method for treating cytomegalovirus infection in a mammal, including human, comprising administering thereto an effective amount of a compound of formula 1 according to claim 1, or a therapeutically acceptable salt thereof.
15. A method for protecting human cells against cytomegalovirus pathogenesis comprising treating said cells with an anti-cytomegalovirus effective amount of a compound of formula 1 according to claim 1, or a therapeutically acceptable salt thereof.
16. The compound of formula 1 according to claim 1 in combination with another anti-herpes compound selected from the group consisting of ganciclovir, forscarnet, acyclovir, valacyclovir, famciclovir, cidofovir, penciclovir, and lobucavir.
17. The compound of formula 1 according to claim 1 in combination with another anti-retroviral compound selected from the group consisting of reverse transcriptase inhibitors and protease inhibitors.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 98/00953

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D205/08 A61K31/395		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 02579 A (ZENECA LIMITED) 26 January 1995 cited in the application see the whole document ---	1,13
A	EP 0 337 549 A (MERCK & CO) 18 October 1989 see the whole document & US 5 229 381 A cited in the application ---	1,13
A	GB 2 266 527 A (MERCK & CO INC.) 3 November 1993 see the whole document ---	1,13
-/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 23 December 1998		Date of mailing of the international search report 07/01/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Kyriakakou, G

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 98/00953

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

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